Center for Theoretical Biology

Report on NASA Grant NGR 33-015-016

for 1968



Faculty of Health Sciences
State University of New York at Buffalo
4248 Ridge Lea Road
Amherst, N. Y., 14226

CONTENTS

# INTRODUCTION

The work of the Center, carried out with assistance from Grant NGR 33-015-016, has involved forty faculty members, fourteen research associates, eighteen graduate students, and six visiting professors. Details of this work are included in the subsequent pages.

During the year a number of undergraduate students have become associated with the Center, and it is anticipated that many students working on independent study programs will be associated with the Center during 1969. Thus, there is a progressive development of our teaching program based upon an enthusiastic research based faculty.

J. F. Danielli

## II. ORGANISATION OF THE CENTER FOR THEORETICAL BIOLOGY

Director: J. F. Danielli

Assistant Director: K. N. Leibovic 1967-1968
R. Rosen 1968-1969

EXECUTIVE COMMITTEE: Maintains relationship between various departments, provides guidance for the programs of Center, and determines budget policies.

J. F. Danielli - Chairman

S. Geisser

J. Bergantz

T. Wu

J. Myhill

F. Snell

D. Murray

ACADEMIC COMMITTEE: Determines the academic policy of the Center, academic research programs, teaching activities, and postdoctoral training.

J. F. Danielli - Chairman

K. N. Leibovic

R. Rosen

R. Rein

K. Jeon

J. Hamann

D. J. Triggle

V. S. Vaidhyanathan

D. A. Cadenhead

P. Bright

J. Borst

L. M. Bianchi

SEMINAR, LIBRARY PUBLICATIONS COMMITTEE: Schedules seminars, special lecture series and symposia, administers the library, publishes the Quarterly Bulletin from the Center.

K. N. Leibovic - Chairman
P. Bright
L. Bianchi
R. Spangler
D. J. Triggle
J. Hoffman
J. Howell
D. C. Wobschall
G. R. Blakley
M. May

BUDGET COMMITTEE: Meets quarterly to discuss appropriations and expenditures of funds provided for the Center.

J. F. Danielli - Chairman
H. Collins
P. Ford
R. Wagner
R. Rosen
D. J. Triggle

GENERAL PURPOSES COMMITTEE: Meets once a month and is responsible for all services, supplies, rooms, complaints, etc.

H. Collins - Chairman
R. Wagner
P. Ford
K. Maher

EXTERNAL ADVISORY COMMITTEE: This is a group of distinguished outside consultants who meet once a year at the Center for Theoretical Biology to evaluate the progress of the Center and advise on future plans.

M. Berman

H. W. Emmons

O. Schmitt

T. L. Hill

E. C. Pollard

FRONTIERS OF RESEARCH COMMITTEE: The function of this study group is to consider the aspects of Biology not presently under study in the Center, particularly novel aspects, and to make recommendations as to whether a serious research effort should be made by the Center in such novel areas.

J. F. Danielli - Chairman

M. Danielli

K. N. Leibovic

R. Rosen

F. Snell

E. Barnard

S. Ohki

A. Isihara

J. Howell

Mac Hammond

V. S. Vaidhyanathan

N. Goel

J. R. Hamann

COLLEGE STUDY GROUP: Met from December, 1967 - May, 1968, when it was dissolved. Ideas were presented and discussed, for a variety of colleges which could be developed on the new campus.

J. F. Danielli - Chairman

M. Danielli

V. S. Vaidhyanathan

R. Spangler

T. Bardos

M. Hammond

A. Maddock

E. Sproul

S. Smith

M. May

P. Ford

## III. FACULTY AND FIELDS OF INTEREST

**Professors:**

| | |
|---|---|
| Thomas Bardos | Cancer chemotherapy |
| Eric A. Barnard | Active centers of enzymes, properties of enzymes in cells |
| Lyle Borst | Physics |
| James F. Danielli | Membrane phenomena, cell theory, cytoplasmic inheritance, relational biology |
| Robert J. Good | Surface chemistry and physics |
| Joseph G. Hoffman | Quantitative measurement of heat released by mammalian tissue cells |
| Akira Isihara | Statistical mechanics |
| Arnold I. McMullen | Theoretical aspects of the physics of intra- and inter-molecular interactions |
| David Pressman | Biochemistry and immunology |
| Robert Rein | Quantum chemistry of organic and biomolecules |
| Irving H. Shames | Continuum mechanics |
| Fred M. Snell | Transport and membrane phenomena, nonequilibrium thermodynamics, theoretical biology |
| Dov Tamari | Algebra; furthering mathematical thought in biology |
| Sol W. Weller | Heterogeneous and homogeneous catalysis; chemical reaction kinetics |
| David A. Yphantis | Biology |
| Marvin Zelen | Statistics |

Associate Professors:

| | |
|---|---|
| Robert Abbott | Surface physics; physisorption and chemisorption of molecules and macromolecules on solid surfaces |
| G. R. Blakley | Population studies |
| David A. Cadenhead | Surface chemistry-monolayer studies and molecules of biological interest |
| Mac S. Hammond | Linguistics and poetics |
| Peter Hebborn | Anti-inflammatory agents - cancer chemotherapy |
| K. Nicholas Leibovic | Processes of communication and control in biological systems especially the central nervous system |
| A. D. MacGillivray | Perturbation theory, including its application to macro-molecular systems |
| Donald C. Mikulecky | Membrane phenomena; nonequil-ibrium thermodynamics transport across biological membranes |
| Charles Paganelli | Transport across biological membrane |
| Armin Ramel | Biochemical Pharmacology |
| Robert Rosen | Biological systems analysis |
| David J. Triggle | Theories and mechanisms of drug-receptor isolation |
| V. S. Vaidhyanathan | Statistical mechanics, membrane transport interfacial physics, mathematical biophysical chemistry |

Assistant Professors:

| | |
|---|---|
| Luigi M. Bianchi | Central nervous system and sensory communication |
| Moises Derechin | Protein structure. Relation between configuration and activity |

| | |
|---|---|
| Kwang W. Jeon | Cytology and cell physiology |
| John F. Moran | Mechanisms of drug action, deuterium isotope; effects in biological systems; receptor isolation |
| Dorita A. Norton | X-ray studies in sterols |
| Shinpei Ohki | The structure and the permeability of membranes |
| Cora G. Saltarelli | Physiology and genetics of pathogenic yeasts; bioengineering |
| Robert A. Spangler | Irreversible thermodynamics, biological transport processes |
| Darold C. Wobschall | Electrical properties of membranes and organic semiconductors |
| Marian May | Assistant to the Director of the Center for Theoretical Biology, and writer for the Center |
| Jon R. Hamann | Relational systems |

Research Associates:

| | |
|---|---|
| John D. Abernethy | Central nervous system and sensory communication |
| Robert Beckwith | Musicology, psycholinguistics - communications theory |
| Peter B. Bright | Theoretical foundations of transport phenomena for the study of neuronal membranes |
| Shym S. Chatterjee | Medicinal organic chemistry |
| Mary Danielli | Anthropological studies bearing on man's control of environment and of his reaction to it |
| Jon R. Hamann | Structure of Science, Pharmacology Quantum Theory |
| James Harlos | Cancer research scientist |
| Andrew Hilgartner | General semantics |

| | |
|---|---|
| Michael Kleiner | Cancer research scientist |
| Marian May | Estrogen receptor isolation and identification |
| Fred Ridley | Medicinal organic chemistry; heterocyclic synthesis; drug-receptor interactions |
| Joan Lorch Staple | Nucleo-cytoplasmic relationships in protozoa and other cells |
| S. R. McLean | Medicinal Organic Chemistry |
| V. C. Swamy | Pharmacology of Adrenergic Receptors |

Graduate Assistants:

Howard Allen

Ehud Artzy

Francis Bellino

John Bircher

John Borst

Michael Davids

Richard Demchak

Joseph Goren

J. S. Jay

Thomas Mathieson

George Pack

Joel Pursner

James Rabinowitz

Nassir Sabah

Robert Sayre

Joseph Smith

Lynn Spees

Miki Wadati

Visiting Professors:

| | |
|---|---|
| Dennis Chapman | Molecular Biophysics |
| Alan Goldup | Lipid Bilayers |
| Herbert Landahl | Mathematical Biology |
| Samuel Levine | Mathematics |
| Michael Pollak | Quantum Biochemistry |
| Paul Weiss | Developmental Biology, specifically neurogenesis |

Consultants:

| | |
|---|---|
| Narendra Goel | Statistical mechanics |
| Sasa Svetina | Intermolecular forces, cell-cell interaction, quantum and statistical study of DNA |
| Martynas Ycas | Molecular biology and cell physiology |
| Miriam Weller | Psychiatric social worker |
| M. H. F. Wilkins | Biophysics |

SUPPORT STAFF

| | |
|---|---|
| Harry Collins | Laboratory Manager |
| Paulette Davis | Key Punch Operator |
| Dennis DeGweck | Computer Programmer |
| Shirley Drescher | Model Builder |
| Priscilla Ford | Administrative Assistant |
| Thomas Maddocks | Instrument Maker |
| Kathleen Maher | Supervising Secretary |
| LaVerne O'Neil | Secretary to the Director |
| Noreen Ritchie | Literature Searcher |
| Margaret I. Smith | Secretary to Assistant Director |

| | |
|---|---|
| Hsin-yu Wang | Computer Programmer |
| Robert Wagner | Accountant and Assistant to the Provost of Natural Sciences and Mathematics |
| Evelyn M. Wood | Artist |
| Charles J. Volk | Photographer and Model Builder |

| Technicians: | Secretaries: |
|---|---|
| Mary O'Hagen | Betty Barry |
| Ruth Morgan | Ursel Busch |
| Lorraine Powers | Joyce Cioch |
| Eleanor Sattler | Lee Gordon |
| | Ruth Harvey |
| | Enez King |
| | Ruth Kuhfahl |
| | Doris Mertens |
| | Alice Richards |

# WORKING PARTY REPORT

# NUCLEAR AND CYTOPLASMIC INHERITANCE

Chairman K. Jeon

# ANNUAL REPORT FROM WORKING PARTY ON NUCLEAR AND CYTOPLASMIC INHERITANCE

1. DEFINITION OF FIELD OF INTEREST:

The genetic control in amoebae, with special emphasis on phenotypic changes.

2. FINANCIAL SUPPORT:

USPHS Grant GM 11603 of NIH

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| K. W. Jeon | Working Party Chairman<br>Research Associate,<br>School of Pharmacy |
| J. F. Danielli | Professor of Theoretical Biology,<br>Biophysics Department, School<br>of Pharmacy, Department of<br>Biology |
| J. F. Moran | Assistant Professor, Biochemistry<br>School of Medicine |
| I. J. Lorch | Research Associate<br>School of Pharmacy |

4. RESEARCH PROGRAM:

The main subject of research during this year has been the mechanism for phenotypic changes that occur in amoebae. Amoebae are completely asexual, and have a large number of chromosomes. Since there are no regular changes in the nuclear genome such as are brought about through mating, the nuclear genome should be stable, together with the phenotypic characters which are believed to be under nuclear control. However, the cell characters of amoebae have been found to change easily both

spontaneously and by experimental manipulations. The spontaneous drift and changes of cell characters occur over a relatively long period, i.e. several years. On the other hand, the experimentally produced changes occur within a few cell generations. Such changes can be produced by injection of heterologous cytoplasm and insertion of heterologous nuclei.

The results obtained so far indicate that these changes are caused by a certain factor, which is present mostly in the cell nucleus and influences heterologous amoebae when introduced into the latter. This factor has been identified only in part, and work will continue to characterise it further.

With a continued partial financial support from the Center, H. Allen, a pre-doctoral research fellow, has been studying the hexosamine metabolism in amoebae. His work carried out during this year was mainly on the metabolic pathways of hexosamine, as studied using techniques of chemical analyses, radioautography and liquid scintallation counting.

During the summer months, a student, D. Busch, studied the effects of morphine on amoebae, with the special emphasis on the cellular mechanisms of adaptation and possible dependence of cells once they have been adapted.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. New simple method of micrurgy on living cells, K.W. Jeon and I. J. Lorch, Nature 217, 463 (1968)

2. Nuclear control of cell movement in amoebae: Nuclear transplantation study, K. W. Jeon, Exptl. Cell Res. 50, 467 (1968)
3. Nuclear-[illegible]-cytoplasmic relations in lethal amoeba hybrids, K. W. Jeon, Exptl. Cell Res. in press
4. Micromanipulation of amoeba nuclei, K. W. Jeon, Methods in Cell Physiology (D.M. Prescott, ed.), Vol. IV, in press
5. Seminar entitled "Nuclear-cytoplasmic relationships in amoebae" given in the Biology Department on January 26, 1968
6. Seminar entitled "Nuclear-cytoplasmic relationships in cell transformation in amoebae" given at the Roswell Park Memorial Institute, on July 17, 1968
7. Seminar entitled "Cell heredity studies in amoebae" given at the Center for Theoretical Biology on October 31, 1968

6. MEETINGS ATTENDED:

1. June 24-28, Gordon Research Conference on "Cell Structure and Metabolishm" in Meriden, N.H. (K.W.Jeon)
2. November 11-13, Annual Meeting of the American Society for Cell Biology in Boston, Massachusetts (K.W. Jeon and I. J. Lorch)

# WORKING PARTY REPORT

# MODELS OF THE CENTRAL NERVOUS SYSTEM AND SENSORY COMMUNICATION

Chairman K. N. Leibovic

# ANNUAL REPORT FROM
# WORKING PARTY ON MODELS OF THE CENTRAL NERVOUS SYSTEM & SENSORY COMMUNICATION

## 1. DEFINITION OF FIELD OF INTEREST:

Theory of information processing in the central nervous system, and information transfer.

## 2. FINANCIAL SUPPORT:

This has come primarily from NIH Grant NB-06682 to K. N. Leibovic and R. A. Spangler, a Buswell Fellowship for J. D. Abernethy from the School of Medicine, and to a smaller extent from NASA Grant NGR 33-015-016.

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| K. N. Leibovic | Working Party Chairman; Dept. of Biophysical Sciences School of Medicine |
| R. A. Spangler | Dept. of Biophysical Sciences |
| J. D. Abernethy | Dept. of Biophysical Sciences School of Medicine |
| L. M. Bianchi | Dept. of Physics, and Faculty of Natural Sciences and Mathematics |
| P. B. Bright | Dept. of Biophysical Sciences School of Medicine |
| J. R. Hamann | Dept. of Biophysical Sciences, and Faculty of Natural Sciences and Mathematics |
| H. D. Landahl | Visiting Professor, CTB |
| N. H. Sabah | Dept. of Biophysical Sciences School of Medicine |
| T. Mathieson | Dept. of Biophysical Sciences School of Medicine |

4. RESEARCH PROGRAM:

The work of this group is based on the premise that a better theoretical understanding how the central nervous system works can unify existing data and assist in the search for the physical bases of central nervous system operations. The procedure we have adopted is to try and work our way inward, as it were, along a sensory pathway and from a notion of the processes at one stage, to investigate those at successively later stages. The visual pathway has been chosen as particularly suitable in view of the extensive data available and because its peripheral organization is already so closely related to that of some deeper structures in the CNS.

More specifically we have addressed ourselves to the following problems:

1. The characteristics of the visual "information input" stage.

2. Information processing in the retina.

3. Information processing beyond the retina.

It is necessary also to understand the operations in individual neurons and in network structures. Hence another problem area is:

4. Mathematical descriptions of signal transmission in single neurons and network structures.

The work accomplished is briefly summarized herewith:

I. A Model of the "Information Input" (Leibovic, 1968a)

The nature of the sensory information relayed to the central nervous system naturally depends on the

characteristics of the sense organ. For example, limulus has a receptor mosaic in its ommatidia, each of which has an individual line to the CNS, although each also includes a weighted sum of the responses of neighboring ommatidia. The frog has a receptive field organization very different from limulus, but its eye is stabilized in its head. In man, on the other hand, the eye moves constantly in drifts and saccades (Ditchburn 1961) which are largely involuntary and appear to be pseudo-random.

Receptive fields will often respond to more or less specific stimuli, such as movement or contrast and in general there is a response probability depending on the stimulus (e.g. Maturana, et al. 1960; Barlow, 1964; Hubel and Wiesel, 1965). The information input in man thus appears to be statistical, with the eye movements serving to sample the visual scene. In this context it is interesting to consider the serial input capacity, for which critical flicker fusion frequency (CFFF) may be taken as a convenient measure (Pirenne 1962). For a qualitative model, we take account only of average quantities. Thus, for an average CFFF of 30 cycles/sec a single "input" will occupy 33 msec. The slow drift of the eye, mentioned above, has a mean amplitude of 5' arc and mean duration of 200 msec. Thus, some 6 "inputs" occur during a slow drift and the amplitude of this movement corresponds to about 6 cone diameters. A saccade only lasts about 30 msec. and presumably only plays a stabilizing role, while the statistical scanning is

performed during a drifting motion. It is interesting to observe that there is a short term visual memory (Averbach & Coriell, 1961) which has a span equivalent to the above 6 "inputs". Thus, the latter may be considered as a package which is processed as a whole and transmitted from the retina to higher centers. Further data pertinent to this model concern the periodic activities observed in some preparations; in the retina a periodic burst activity of 20-40 bursts per sec has been observed (Laufer and Verzeano 1967), which is of the same order as the duration of one input; in the LGN a periodicity of between 100 to 200 msec is found (Granit 1962), which is of the same order as a "package" of 6 "inputs".

II. Information Processing in the Retina (Leibovic 1968b, in press, K. N. Leibovic, R. A. Spangler, J. D. Abernethy, in preparation)

In order to analyze the manner in which the statistical input is handled in the retina, it is necessary to have a mathematical description of the operations in the retinal nerve net. To this end, we considered the response characteristics of ganglion cells on which a detailed experimental investigation is available by Rodieck and Stone (1965 a,b) for the cat. Rodieck's (1965) model was examined and though adequate as a first approximation, it failed to account for some response features shown in the experimental records. We, therefore, proposed an alternative model in which there are 3 response components in a

receptive field with a "center-surround" organization; 2 components determine the "center" response and the third the "surround" response. Each component has a distribution of a response strength across a receptive field diameter, weighted by the factor [a exp $(-b^2)$], where x is distance from the receptive field center. The whole receptive field is divided into responsive units and, for example, the ganglion cell response of an "on-center" cell to a spot stimulus on a responsive unit at a distance x from the center is

$$R(I,\Delta I,x,t) = \sum_{i=1}^{3} u \left[(-1)^{i-1}\rho_i\right] \rho_i(I,\Delta I,x,t)$$

where,

$I$ = background level of illumination

$\Delta I$ = increased illumination due to spot

$\rho_i$ = response components; i = 1,2,3.

$$u(\alpha) = \begin{matrix} 1, & \alpha > 0 \\ 0, & \alpha < 0 \end{matrix}$$

and

$$\rho_i(I,\Delta I,x,t) = r_{iu}[x, I+u(t-t_{io})\Delta I] + u(t-t_{io}) r_{it}(x,I,\Delta I)\exp\left(-\frac{t-t_{io}}{\tau_i}\right)$$

with

$r_{im}$, $r_{it}$ = maintained, transient response levels respectively

$\tau_i$ = time constant

$t_{io}$ = latent period

The model is nonlinear; each response component rises or falls instantaneously on stimulation, depending on the polarity of the stimulus; moreover, each response component

saturates in such a manner that an excitatory (inhibitory) component cannot become negative (positive). Computer simulation of ganglion cell responses to moving and stationary patterns has yielded satisfactory agreement with experimental results.

The different response components of our model might be assigned to different neural pathways in the retina. This problem, however, remains under investigation at the present time. It is related to structure and function of which another aspect concerns the anatomical basis of the observed variation of ganglion cell response when a spot of light is moved along a receptive field diameter. We have investigated this with the following result:

It is known, e.g. in the cat, (Brown and Major 1966) that the "center" of the receptive field coincides with the extent of the dendritic tree of the ganglion cell. While the neural net between receptors and ganglion cell is quite complex, we decided to regard it as uniform as far as response strength is concerned. Then, on the assumption of a uniform distribution of synaptic inputs at the level of the ganglion cell, the response strength would only depend on the ganglion cell's membrane area available for synaptic signals. We obtained estimates of ganglion cell membrane area from the published data and compared this with the experimental findings of response as a function of spot stimulus position. The agreement of these two sets of data was very good and, moreover, they were approximated well by a "Gaussian" curve. We have

discussed in our papers the possible biological significance of this from the point of view of optimal detection. We conclude that the geometry of ganglion cell dendritic tree accounts primarily for the observed response to a spot stimulus, when the latter is moved across a receptive field diameter.

III. Information Processing Beyond the Retina (K. N. Leibovic, 1968b)

Under this heading we have previously been concerned with the application of geometric probability to a model of visual size perception. Further progress, however, is difficult in the absence of a better understanding of the operations in the LGN and visual cortex. For, in spite of the increasing amount of work of recent years on the LGN and visual cortex (see e.g. Bishop 1967 for a review) there is still a relative scarcity of experimental data beyond the retina, which is directly suitable for theoretical models of information processing. We have, therefore, adopted the following approach: Knowing what information cannot be represented at the retinal level in the responses of individual ganglion cells, we ask how these responses might be combined to yield some of the perceptual variables of which we are aware. The following is an example of this approach.

Since many receptor cells contribute to the response of a single ganglion cell, the latter cannot respond uniquely to different positions and intensities of even so simple a stimulus as a small spot of light. While limulus may

retain the information contained in the fine grain of its ommatidial mosaic in individual optic nerve fibers, frog and man cannot, due to the organization of their receptive fields. The variation of the ganglion cell response to a spot in different positions of the receptive field has already been discussed. The response also varies with intensity, of course. It can then be shown that at least three overlapping receptive fields are needed to identify uniquely the position and intensity of the spot of light. The analysis assumes circular receptive fields and neglects the input statistics and eye movements. But the argument is interesting in its demonstration that the overlapping of receptive fields is not simply a device to get increased reliability through redundancy. The areal spread of the receptive field is necessary to perform the logical operations in the neural net between receptors and ganglion cells and overlap reflects the need of dealing with a statistical input, but at the same time, new perceptual variables can be obtained at a higher level due to overlapping. There is another important observation which follows from this example. There has been an argument for some time, whether perceptual variables are represented in the activity of single neurons or groups of neurons in the C. N. S. Our argument shows that at least three neurons are required at the retinal level to represent position and intensity and if this kind of information is to be represented in single neuron activity in the C.N.S. it would soon lead to the

need for an impossibly large number of neurons.

All this is pertinent to the kind of operations which might be performed in the networks of the LGN or visual cortex.

IV. Signal Transmission in Single Neurons and Network Structures (K. N. Leibovic and N. H. Sabah, in preparation)

There are many puzzles of operations in neural nets which cannot be resolved at present. For example, if one thinks of psychophysiology, it would be nice to be able to say what goes on in the retinal network during the course of dark adaptation or in visual masking phenomena. Many retinal neurons probably do not sustain all-or-none spikes and some synapses look neither like chemical synapses nor like tight electric junctions in the electron microscope.

To understand synaptic and membrane signals better, we have begun a theoretical study.

From published data of endplate potentials (Katz, 1962) and experimental curves of presynaptic vs. post-synaptic depolarization (Katz and Miledi 1967) we have developed a mathematical expression for the latter, using drug-receptor interaction theory (D. J. Triggle 1965). We have also proposed (for non-"chemical" synapses) a possible mechanism of synaptic interaction mediated by $K^+$ in the intercellular space.

With regard to membrane signals, we have investigated a cable model in which a modified set of Hodgkin and Huxley

equations are used. These have their ionic conductances adjusted in such a way, that "all-or-none" spikes cannot be generated. We have found that graded pulses can be produced, which we have named "g-pulses" to distinguish them from electrotonic signals on the one hand and "all-or-none" spikes on the other. These "g-pulses" can either decay or grow in amplitude up to a certain point, depending on conditions. They have also some interesting properties in terms of space constants. The significance of "g-pulses" lies not only in their possible occurrence in the retina, where spikes and curious spike-like signals have recently been recorded (e.g. Tomita 1967), but also to their possible transmission in dendrites: for example, spike-like signals have recently been recorded from the dendritic trees of cerebellar Purkinje cells (Llinás, 1968).

Finally, we have begun a study of the possible functional significance of network structures like reciprocal synapses - which are found in the retina - and also of recurrent collaterals and small networks such as exist between receptor cells, horizontals and bipolars in the retina. Some preliminary results have been obtained as discussed in the paper quoted above (K. N. Leibovic and N. H. Sabah, in preparation).

## V. Neural Nets

One of the central themes in brain research is the problem of how to explain the global behavior of the brain or of its suborgans as the resultant of the

behavior of single neurons plus their mutual interaction. The approach to such problems has been frequently blurred by the seemingly diffuse failure to recognize the need of hierarchical inferential methods in going from the neuronal level to that of the organ. L. M. Bianchi and J. R. Hamann have investigated a very general procedure for the foundation and justification of statistical methods in the description of neural nets, considered as particular cases of relational systems. It has been shown conceptually how many interesting aspects of the behavior of neural nets, specifically those far from equilibrium and stationarity, can be meaningfully approached.

VI. Physio-Psychological Studies

The problems of perception and cognition (the claim that to perceive is to know still far from being settled) are clearly in need of foundational studies. We have an enormous amount of data which is extremely heterogeneous with respect to both the levels at which they are obtained and the experimental conditions prevailing within each level. It is very often impossible to speak of pure modes of operation due to the strong interactions among various modes (e.g., verbal and visual).

The problem of how the various stages in the sensory pathways process incoming information and lead to the storage of some image of it is also the problem of demonstrating the continuity and the consistency among and within the different organizational levels. L. M. Bianchi and J. R. Hamann have started an investigation of

these problems within the framework of relational systems. L. B. Bianchi has also been interested in the temporal aspects of sensory input processing, particularly in vision. He has considered the question of which elementary "features" are physiologically represented as neural activity and how these are combined into the psychological features usually associated by man to a stimulus. Some partial answers to this problem can be given by an analysis of the fragmentation phenomena in stabilized vision. In collaboration with Dr. R. M. Pritchard's group at McMaster University, L. M. Bianchi has been investigating such phenomena using particular geometrical patterns (Garner's matrices).

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Neural Nets as Relational Systems", L.M.Bianchi & J.R. Hamann, Quart. Bul. Center Theoret. Biol. 1, No. 2, 81 (1968)
2. "Relations Between Component and System Behavior", selected for publication from papers presented at the Bionics Symposium, 1966, pp. 649-654 in Cybernetic Problems in Bionics, Gordon and Breech, London and New York, 1968 (P. B. Bright)
3. Leibovic, K. N., J. Gen. Psych., 78:19, 1968a
4. Leibovic, K. N., J. Theor. Biol., (In press) 1968b

References:

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2. Barlow, H. B., Hill, R. M., Levick, J. Physiol., 173:337, 1964

3. Bishop, P. O., Ann. Rev. Physiol., 29:427, 1967

4. Brown, J. E., Major, D., Exp. Neurol., 15:70, 1966

5. Ditchburn, R. W., N.P.L. Symposium on Visual Problems of Color, Vol. 2, Chem. Pub. Co., N.Y.,1961

6. Granit, R., in H. Davson (Ed.), "The Eye", Vol. 2, Academic Press, N.Y., 1962

7. Hubel, D.H., Wiesel, T.N., J. Neurophynol., 28(2):229, 1965

8. Katz, B., Proc. Roy. Soc. B., 155:455, 1962

9. Katz, B., Miledi, R., J. Physiol., 192:407, 1967

10. Laufer, M., Verzeano, M., Vision Research, 7:215, 1967

11. Leibovic, K.N., Bull. Math. Biophys., 27:305, 1965

12. Leibovic, K.N., Biophys. Soc. 10th Annual Meeting, 1966a.

13. Leibovic, K.N., J. Theor. Biol., 11:112, 1966b

14. Leibovic, K.N., 2nd. Inter. Biophys. Cong., Vienna, 1966c.

15. Leibovic, K.N., Gordon Res. Conf. on Biomath.,1967a

16. Leibovic, K.N., N.Y. Acad. Sc. Conf. on Rein Control, 1967b

17. Leibovic, K.N., Spangler, R.A., 2nd. Inter. Biophys. Congress, Vienna, 1966d

18. Llinas, R., Nicholson, C., Freeman, J.A., Hillman, D.E., Science, 160(3832):1132, 1968

20. Maturana, H.R., Lettvin, J.Y., McCulloch, W.S., Pitts, W.H., J. Gen. Physiol., Supplement, 43:129, 1960

21. Pirene, M.H. in H. Davson (Ed.), "The Eye", Vol. 2, Academic Press, N.Y.

22. Rodieck, R.W., Vision Research, 5:583, 1965

23. Rodieck, R.W., Stone, J., J. Neurophysiol., 28:819, 1965a

24. Rodieck, R.W., Stone, J., J. Neurophysiol., 28:833, 1965b

25. Tomita, R., Personal communication, 1967

26. Triggle, D.J., "Chemical Aspects of the Autonomic Nervous System", Academic Press, 1965

# WORKING PARTY REPORT

# RECEPTOR STRUCTURE, FUNCTION AND ISOLATION

Chairman D. J. Triggle

# ANNUAL REPORT FROM WORKING PARTY ON RECEPTOR STRUCTURE, FUNCTION AND ISOLATION

1. DEFINITION OF FIELD OF INTEREST:

Interactions of neurotransmitters (Norepinephrine and Acetylcholine) with their corresponding receptors and the relationship of this interaction to the subsequent physiological and biochemical responses.

2. FINANCIAL SUPPORT:

NIH (GM 11603, HE 09336)

NASA(NRG 33-015-016)

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| D. J. Triggle | Dept. of Biochemical Pharmacology, Pharmacy |
| J. F. Moran | Dept. of Biochemistry, Medicine |
| J. F. Danielli | Center for Theoretical Biology |
| M. May | Center for Theoretical Biology |
| S. S. Chatterjee | Biochemical Pharmacology |
| V. C. Swamy | Biochemical Pharmacology |
| H. F. Ridley | Biochemical Pharmacology |
| S. McLean | Biochemical Pharmacology |

4. RESEARCH PROGRAM:

Our work has continued to focus on the problem of determining the quantitative relationships between receptor occupation and the physiological response. In

previous reports we have noted our work on the adrenergic α-receptor system. We have now extended the general approach utilized in these studies to the cholinergic (muscarinic) receptor (Section V, Rev. 9). We have demonstrated that, as for the α-receptor system maximum response with the neurotransmitter, acetylcholine, requires 100% occupation of receptors and that response is directly proportional to receptor occupation. However, the situation is more complex since we have provided firm evidence for the existence of two discrete, partially overlapping, binding sites at the acetylcholine receptor. Structure-activity relationships for agonists and antagonists active at this site will have to be reinterpreted on the basis of this finding.

In other areas we have continued our work on the synthesis of rigid and semi-rigid analogs of acetylcholine on the premise that such compounds may give more information concerning the geometry of the receptor binding groups than flexible analogs. Our work in this area in 1968 is represented by publications 2, 6 and 7 (Section V).

5. PUBLICATIONS, PAPERS AND SEMINARS:

1.S. S. Chatterjee and D. J. Triggle, "Synthesis of Azetidin-3-01", Chem. Comm. (1968)

2.M. May and D. J. Triggle, "Studies on the Cholinergic Receptor I", J. Pharm Sci. (1968)

3. M. May, L. Czoncha, D. R. Garrison and D. J. Triggle, "Analgesic, Hypothermic, and Depressant Activities of Some N-substituted-α-5, 9-dimethyl-6, 7-benzomorphans", J. Pharm. Sci., (1968)

4. S. Vickers and D. J. Triggle, "Preparation and Diazotization of Some 0- and p-Aminophenylbenzoates and benzamides", J. Chem. Soc. (C), (1968)

5. J. Hampshire, P. Hebborn, A. M. Triggle and D. J. Triggle, "Potential Folic Reductase Inhibitors. III", J. Med. Chem., 11, 583, (1969)

6. M. May, H. F. Ridley and D. J. Triggle, "Studies on the Cholinergic Receptor. II". J. Med. Chem., Jan. (1968)

7. M. May, H. F. Ridley and D. J. Triggle, "Studies on the Cholinergic Receptor. III", J. Med. Chem., Jan. (1969)

8. J. F. Moran, C. R. Triggle and D. J. Triggle, "Studies on the Adrenergic Receptor. III", J. Pharm. Pharmacol., in press

9. J. F. Moran and D. J. Triggle, "The Quantitation and Isolation of Pharmacological Receptors", Ch. 10. In "Fundamental Concepts in Drug-Receptor Interactions", Ed. Danielli, Moran and Triggle, Academic Press (1969)

10. D. J. Triggle, "The Adrenergic Hormone", Ch. 46 in "Medicinal Chemistry", Ed. A. Burger, J. Wiley (1969)

11. P. Hebborn, T. J. Bardos, Z. F. Chmielewicz and D. J. Triggle, "Miracil D Analogs: DNA-dependent RNA polymerase Inhibitory Activity and In Vivo Biological Activity", Proc. Amer. Assoc., Cancer Res., 9, 29 (1968)

Presentations:

1. D. R. Garrison, M. May, H. F. Ridley and D. J. Triggle, "Studies on the Cholinergic Receptor", Presented to Med. Chem. Section of American Chemical Society Meeting, San Francisco, April,1968
2. S. S. Chatterjee, J. F. Moran, A. M. Triggle, D. J. Triggle and A. Wayne "Folate Reductase Inhibitory Activities of Substituted S-Arylazo-pyrimidines, ACS meeting, San Francisco, April,1968
3. Z. F. Chmielewicz, T. J. Bardos, P. Hebborn and D. J. Triggle, "New Miracil D Analogs", ACS Meeting, San Francisco, April, 1968
4. D. J. Triggle, "Recent Developments in Adrenergic and Cholinergic Receptor Mechanisms", School of Pharmacy, Ohio State University, December 4, 1968
5. J. F. Moran and D. J. Triggle, "The Quantitation and Isolation of Pharmacological Receptors", Symposium on "Fundamental Concepts in Drug-Receptor Interactions", Buffalo, N.Y., Aug. 26-28, 1968

6. MEETINGS:

J. F. Moran and D. J. Triggle organized Third Buffalo-Milan Symposium (sponsored jointly by School of Pharmacy,

SUNY/B and Institute of Pharmacology, University of Milan) on Fundamental Concepts in Drug-Receptor Interactions", Aug. 26-28, 1968 in Buffalo, New York.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

a) D. J. Triggle, participated in Biochemical Pharmacology 405, Biophysics 401, Biophysics 509.

b) D. J. Triggle and J. F. Moran presented Biochemical Pharmacology 630-630R and Biochemistry 630-630R, a two-semester course entitled "Molecular Basis of Chemical Transmission Processes".

c) J. F. Moran, participated in Biochemistry 601.

d) V. C. Swamy, participated in Biochemical Pharmacology 406 L.

# WORKING PARTY REPORT

# STATISTICAL MECHANICS IN BIOPHYSICAL SYSTEMS

Chairman V. S. Vaidhyanathan

# ANNUAL REPORT FROM
# WORKING PARTY ON STATISTICAL MECHANICS
# IN BIOPHYSICAL SYSTEMS

## 1. DEFINITION OF FIELD OF INTEREST:

The fields of interest of members of this working party may be broadly defined as the application of statistical mechanics, thermodynamics and irreversible thermodynamics to biological problems. Individual members' interests are broad and diversified ranging from lipid film stability to the investigation of fundamental problems in statistical mechanics.

## 2. FINANCIAL SUPPORT:

In addition to support from Center funds, a grant from Life Insurance Medical Research Fund was utilised, #G-68-16; 50-1152A.

NASA - NGR 33-015-016; NIH GM11603

Graduate School Grant #50-8694; GU-1864

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| V. S. Vaidhyanathan | Working Party Chairman;<br>Associate Professor, Pharmacy |
| Peter Bright | Research Instructor<br>School of Medicine |
| Shinpei Ohki | Assistant Professor<br>Dept. of Biophysical Sciences |
| Robert Spangler | Assistant Professor<br>Dept. of Biophysical Sciences |
| Fred Snell | Professor, Biophysical Sciences<br>Dean, Graduate School |

Student Participants: Mrs. Wu, Jayanthinathan, R. Sayre

All the above mentioned members of the group are members of the Center for Theoretical Biology and members of the Department of Biophysical Sciences. In addition, Dr. Narendra S. Goel, Department of Physics, University of Rochester; Dr. Ruth S. Aranow, Research Institute for Advanced Studies, Baltimore, and Dr. F. Sauer, Visiting Professor at SUNY/B, and of Max-Planck Institute for Biophysics, Frankfurt, Germany, have participated in both private and public discussions with various members of the group.

4. RESEARCH PROGRAM:

It is difficult if not impossible to describe in the short space given, the research programs carried out by this group, except to state simply that all problems of interest in membrane and transport phenomena are being studied by individual members of the group. The following presentations summarise Vaidhyanathan's interests and the work done mainly in collaboration with Dr. Goel. The programs detailed below are only representative and not exhaustive of the research being carried out by various members. (Individual members current interests are being presented by them in separate reports.)

Research Reports:

STABILITY OF LIPID FILMS IN AQUEOUS ELECTROLYTE MEDIA

As part of our continuing study of the stability of lipid films, the electrostatic energy of charged species acting across a lipid film with aqueous electrolytes on

either side have been quantitatively analysed. Utilising the Fouries-Bessel integral technique, the electrostatic potential at an arbitrary point for a system consisting of two charges on either side of a thin film is determined. These results are being published in a forthcoming paper (in press) in the Journal of Theoretical Biology.

THE ELECTRICAL CONDUCTANCE ACROSS LIPID FILMS.

Since the conductivity of electrolytes in liquids is one of the few transport problems in which satisfactory agreement between theory and experiment has been obtained, we have undertaken a serious systematic analysis of the electrical conductance of electrolytes across membranes containing fixed charges. Our objective is to generalize the results of Onsager and Fuoss to be valid for unsymmetrical electrolytes and for transport across membranes containing fixed charges. Both general and approximate results for the potential of t tal force acting on an ion with finite frictional coefficient due to fixed charge in the system is presented. An iterative procedure for finding the solution of an appropriate differential equation is developed. The differential equations necessary for generalisation of conductance function to many ion system are presented. These equations are further analysed in a separate communication, wherein the partial potential of mobile ion component force is presented. Included in these considerations is the possibility of ion pair formation in low dielectric media.

TIME DEPENDENT PHENOMENA IN MEMBRANES.

The membrane oscillator problem is being further analysed as due to coupling of lattice vibrations with the hydrodynamic motions of solution with the objective of obtaining a theoretical solution for Teorells oscillator. In addition, the possibility of the development of a potential difference across a membrane, due to the solution being subjected to a longitudinal wave motion being imposed by sound waves, is being analysed. Some of the mathematical difficulties encountered in the development of the theory of the Parmenter effect is still being studied.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Stability of Lipid Films in Aqueous Electrolyte Media: Electrostatic Interactions", V. S. Vaidhyanathan and N. S. Goel, J. of Theo. Biol. (in press)
2. "Conductance Function of Electrolyte Transport Across Lipid Films", V. S. Vaidhyanathan, J. of Theo. Biol. (in press)

6. MEETINGS:

Biophysical Society National meeting, in Pittsburgh in February, presented a paper on conductivity across lipid films.

A paper was presented during the conference on Biophysical aspects of permeability in Jerusalem,

Israel, during July. (The paper was presented by Dr. Robert Rein, since Vaidhyanathan could not be present)

Participated in Summer Colloquium on application of statistical mechanics to biology, Traverse City, Michigan, July.

Presented an invited talk in the Symposium on thin films, organized by Colloid and Surface Chemistry division of American Chemical Society during its National Meeting held in Atlantic City, N.J., September.

Participated in the conference on Membrane Proteins, organised by the American Heart Association, New York, November.

7. CONTRIBUTION TO UNIVERSITY TEACHING:

Coordinated Biophysics 511-512 during year '67-'68.

Gave lectures in Biophysics 401, Fall, '68.

Held a series of seminars as part of the Working Party in Statistical Mechanics.

8. MISCELLANEOUS ACTIVITIES:

Participated as a member: Academic Committee of CTB
Frontiers of Science
College Study Group

Refereed number of papers: Journal of Physical Chemistry
Biophysical Journal
Journal of Theoretical Biology

# WORKING PARTY REPORT

# SYMBOLIC RELATIONAL SYSTEMS

Chairman: J. R. Hamann

# ANNUAL REPORT FROM

# WORKING PARTY ON SYMBOLIC RELATIONAL SYSTEMS

## 1. DEFINITION OF FIELD OF INTEREST:

This working party is concerned with the biological aspects of symbolic relational systems (especially, symbolic behavior).

## 2. FINANCIAL SUPPORT:

N.A.S.A. Grant No. NGR 33-015-016

N.I.H. Grant No. GM 11603

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| Jon Ray Hamann | Working Party Chairman; Assistant Professor, Faculty of Natural Sciences and Mathematics; Department of Biophysical Sciences, School of Pharmacy. |
| Robert Beckwith | Research Associate School of Music |
| Luigi M. Bianchi | Assistant Professor, Faculty of Natural Sciences and Mathematics; Department of Physics. |
| John Borst | Research Assistant and Graduate Student, Department of Biophysical Sciences |
| Mary Danielli | Research Associate School of Pharmacy |
| Richard Danielli | Research Assistant School of Pharmacy |

| | |
|---|---|
| Mac Hammond | Associate Professor, Department of English, Faculty of Arts and Letters |
| David G. Hays | Chairman, Department of Linguistics Faculty of Social Sciences and Administration |
| C. Andrew Hilgartner | Senior Research Associate School of Pharmacy |
| Erwin M. Segal | Associate Professor, Department of Psychology, Faculty of Social Sciences and Administration |

4. RESEARCH PROGRAM:

The working party on Symbolic Relational Systems is a newly formed group resulting from a need established via a prior investigation in the Frontiers of Science Working Party, and from two previously existing informal programs interested in the structure of science (J. R. Hamann) and in unified approaches to physiology, psychology and biology (L. M. Bianchi). While its motivation and goals are already well defined, its mechanics is still in a process of clarification.

A. Relational Systems.

A major effort is being undertaken to investigate the foundational problems of traditional and recent fields of science, from physics to biology, from psychology to sociology and economics, using the relational systems approach.

In particular, J. R. Hamann and L. M. Bianchi have considered the question of the applicability of statistical mechanical methods to population dynamics in ecology and to neural nets. One important and general result is a proof that a suitable stochastic formulation of highly multiple interacting systems subsumes Gibbs statistical mechanics as applied to such systems.

B. Biological Aspects of Theoretical Musicology.

An important symbolic system whose biological relevance has almost gone unnoticed in the past is that of music. R. Beckwith has initiated a study of musical improvisation in its relation to verbal discourse and interactive symbolic behavior in general. He plans also to investigate the perceptual-cognitive processes involved in music understanding (with some possible implication for computer composition). A series of seminars on these subjects is being planned for the Spring, 1969. Also, a research program directed at the development of new operational procedures for "transformational" melodic analysis is being proposed.

C. Chemistry

R. Danielli and J. Hamann are working on a relational systems formalization of physical chemistry. With L. Bianchi they are also working on the initial development of an approach to bimolecular kinetics similar to the Voleterra-Lotka-Kerner approach in ecology.

D. Human Behavior

A. Hilgartner has been involved in the study of the interactions between human behavior and symbolic systems. He has elaborated a set-theoretic formulation of the structure

of human psycho-dynamics. The theory is currently being extended to show the mechanisms of action of psychotherapy, and to apply its logical language to the topic of bio-chemical mechanisms of control of metabolism.

E. Anthropology

M. Danielli has long been involved in elucidating the psycho-social implication of the geomantic diagrams of Madagascar. Present attempts are underway to extract the relational meaning of such diagrams.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Neural Nets as Relational Systems", L. M. Bianchi and J. R. Hamann, Quart. Bull. CTB, 1, No. 2, 81 (1968)

2. "Stochastic Population Mechanics in the Relational Systems Formalism: Volterra-Lotka Ecological Dynamics", J. R. Hamann and L. M. Bianchi

6. MEETINGS:

1. "Summer Colloquium on Theoretical Biology and Biophysics: Applications of Thermodynamics and Statistical Mechanics to Biology". Traverse City, Michigan, July 1-31, 1968. The Colloquium was sponsored by NASA and directed by H. Morowitz.

2. Symposium on Information Processing in the Nervous System. SUNY/B, October 21-23, organized by K. N. Leibovic.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

1. Members of the working party have taken part in the organizing and teaching of two freshman seminars, (Science" Order and Disorder" and "Experiential Approaches to Science"), NSM 199 A & B.

8. MISCELLANEOUS ACTIVITIES:

1. See ORGANIZATION OF THE CENTER FOR THEORETICAL BIOLOGY and REPORT FROM CENTER COMMITTEES.

2. Refereeing of manuscripts for Journal of Theoretical Biology, Bulletin of Mathematical Biophysics, and Biophysical Journal.

# WORKING PARTY REPORT

# SYSTEM THEORY AND RELATIONAL BIOLOGY

Chairman: R. Rosen

# ANNUAL REPORT FROM WORKING PARTY ON SYSTEM THEORY AND RELATIONAL BIOLOGY

## 1. DEFINITION OF FIELD OF INTEREST:

The basic problem with which this working party is concerned is that of functional organization in biological systems; how such descriptions can be effectively made, and dynamical predictions drawn from them. The systematic study of relational models is relatively new, but it is already clear, we believe, that such relational studies have already proved their worth, both in generating important new biological insights, and in indicating several new areas for mathematical investigation.

## 2. FINANCIAL SUPPORT:

The operating budget of this working party is presently constituted from Center funds. A large-scale proposal ($150,000 over a 3-year period) is presently pending at NIH.

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| Robert Rosen | Working Party Chairman, Associate Professor of Biophysics and Mathematics, |
| J. F. Danielli | Director, Center for Theoretical Biology |
| K. N. Leibovic | Associate Professor, Dept. of Biophysics |

| | |
|---|---|
| J. Myhill | Professor, Department of Mathematics |
| A. Ralston | Director and Professor, Computer Services |
| H. Martens | Professor, Electrical Engineering |

4. RESEARCH PROGRAM:

The research program of the working party can be described in terms of four distinct but inter-related projects:

A. Relational Models of Cellular Systems. Under this heading is comprised work on specific relational models (the (M, R)-systems), the mathematics appropriate to the study of these models, and the manner in which relational predictions can be compared with experimental results on real systems.

B. Analysis of Regulatory and Control Mechanisms in Biological Systems. Though conceptually close to the problems described above, the main problem here is to identify the stability properties of biological systems described through systems of differential equations, and to recast the concepts of regulation and control in terms of stability and structural stability in dynamical systems. An important product of this work has been to discover the limitations inherent in external dynamical descriptions, which bears directly on the basic notions of reductionism in biology, and which has raised new and, we believe

important questions of a purely system-theoretic character. (ref. 2)

C. Optimal Design as a General Biological Principle. The problems here concern (a) the characterization of specific biological structures (e.g. the vascular system of vertebrates) in terms of minimal principles, with a view particularly towards the evolutionary development of these structures, and (b) the more general theoretical application of optimality principles to enable relational models to make direct contact with experiment. Succinctly stated, the difficulty in relating relational arguments to experimental information is that the relational arguments generally characterize an entire class of physically diverse but dynamically equivalent (i.e. analogous) systems, while experimental information typically concerns only a single system in such a class. It is characteristic of optimality principles that they pick one (or a few) specific systems from a class of relationally equivalent systems (i.e. optimality provides an additional constraint); systems satisfying such an additional constraint may be studied in far greater structural detail, and in this way, it is believed that their structural properties can be directly compared with experiments on real systems.

D. Pattern Formation in Developing Systems. The basic problems here arose in experimental work on re-aggregation ("sorting-out") of populations of dissociated embryonic cells. We attempt to characterize those patterns which can arise in model systems possessing the basic properties of motility and selective adhesiveness (Malcolm Steinberg),

and, more generally, to determine what the implications of sorting-out phenomena tell us about morphogenesis in the intact embryo.

(NOTE: The remaining responses concern only Robert Rosen The activities of other members of the working party are described under the primary affilitations of those members).

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Recent Developments in the Theory of Control and Regulation of Cellular Processes". Int. Revs. Cytology (Danielli & Bourne, eds.) vol. 23, 1968, 25-88. Academic Press.
2. "On Analogous Systems". Bull. Math. Biophysics. 30 (1969), 481-492.
3. "Turings Morphogens, Two-Factor Systems and Active Transport". ibid. 493-499.
4. "Some Comments on the Physico-Chemical Description of Biological Activity". J. Theoret. Biol. Vol. 18, #3 (1968), 380-386.

6. MEETINGS:

The only meetings attended during the past year were the IFAC International Symposium on Technical and Biological Problems of Control, Yerevan USSR, Sept. 24-28, 1968, and the American Society for Cell Biology Meetings, Boston, Nov. 11-13, 1968.

7. MISCELLANEOUS ACTIVITIES:

1. Editing a comprehensive multi-volume text-book on mathematical biology for Academic Press.
2. Preparing a textbook on Dynamical Systems in Biology, to appear in the Wiley series on Bioengineering (edited by John Milsum).
3. Membership on a number of University committees, concerned primarily with program and curriculum development, (particularly in Applied Mathematics), and chairmanship screening (Mathematics and Biology Departments).
4. Since October 1968, Assistant Director, Center of Theoretical Biology.

# WORKING PARTY REPORT

# THEORETICAL PHARMACOLOGY

Chairman: J. R. Hamann

# ANNUAL REPORT FROM WORKING PARTY ON THEORETICAL PHARMACOLOGY

## 1. DEFINITION OF FIELD OF INTEREST:

Theoretical studies on drug structure and action, in particular, quantum mechanical treatment of electronic structure - pharmacological activity relations.

## 2. FINANCIAL SUPPORT:

Center funds from N.A.S.A. Grant No. NGR-33-015 -016; a Grant from the Committee on Research and Creative Activity, Graduate School, SUNY/B; and a Grant from the United Health Foundation, UHF Grant No. G-F-68-UB.

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| J. R. Hamann | Working Party Chairman; Assistant Professor, Faculty of Natural Sciences and Mathematics, and Department of Biophysical Sciences, School of Pharmacy |
| L. M. Bianchi | Assistant Professor, Faculty of Natural Sciences and Mathematics, and Department of Physics |
| J. Borst | Research Assistant, and Graduate Student, Department of Biophysical Sciences School of Pharmacy |
| W. Giordano | Physician and Clinical Pharmacologist, Twin Lakes, Wisconsin |
| A. Hedley | Research Assistant |

| | |
|---|---|
| J. Olsen | Research Associate, New York University and Staten Island Community College |
| B. Petersen | Research Assistant |
| D. J. Triggle | Associate Professor, Department of Biochemical Pharmacology and Biophysical Sciences, School of Pharmacy |
| V. S. Vaidhyanathan | Associate Professor, Department of Biophysical Sciences, School of Pharmacy |

4. RESEARCH PROGRAM:

The sequence of steps involved in this continuing theoretical study is as follows:

1. Quantum mechanical determination of intra- and inter-molecular structure
2. The statistical mechanical conversion of this molecular information to bulk phase data
3. Thermodynamic prediction and correlation
4. Through the conjunction of the theoretical and experimental biomolecular data, "phenomenological" relations should be deducible upon which particular pharmacodynamical theories can be formulated.

The work presently in progress is concerned numerically with the first step and conceptually with the remaining three states.

The principle systems under investigation are the cholinergic system and, in collaboration with Professor

J. P. Green, Department of Pharmacology, Mt. Sinai Medical School, N. Y., N. Y., the "N.I.H. Shift" in the biological amines. On the former we are studying each of the three classes the cholinomimetics, the cholinesterase inhibitors, and the reactivators. The studies on the NIH-Shift have initially entailed the quantum mechanical elucidation of the energetically favored isolated molecular conformations of the amino acids involved.

5. PUBLICATIONS, PAPERS, AND SEMINARS:

]] A preliminary report of the results obtained by J. Borst, A. Hedley, B. Petersen, and J. R. Hamann on the reactivation problem will be presented as

1. "Molecular Orbital Studies of the PAM Acetylcholinesterase Reactivators", Q.B.C.T.B., Vol. 1, 2 (1969)

The following manuscripts by J. Olsen, J. P. Green and J. R. Hamann represent the work completed this year on the "NIH-Shift" problem:

1. "Total Valence Electron Calculations. I. Dipolar Ion of Phenyl Alanine"
2. "Total Valence Electron Calculations. II. The Dipolar Ion of Tryptaphane"
3. "The Conformations of Acetanalide as Determined By Total Valence Electron Calculations".
4. "Total Valence Electron Calculations of Acetanalide, Population Analysis"

5. "Total Valence Electron Calculations on the "NIH-Shift"

The Third Annual Buffalo-Milan Symposium on Molecular Pharmacology - "Fundamental Concepts of Drug-Receptor Interactions" - Chairman, D. J. Triggle; was attended by L. M. Bianchi, W. Giordano and J. R. Hamann.

The following lectures were directly relevant to the activities of this Working Party. (See the reports of other Working Parties for related listings).

1. "Intramolecular Electronic Structure Activity Studies in Pharmacology", lecture presented in the Department of Pharmacology, SUNY/B February 1968.
2. "Quantum Mechanical Studies of Electronic Structure-Activity Relations in Pharmacology", lecture presented before the Washington-Maryland Section of the Amer. Chem. Soc. "Meeting in Miniature", Univ. of Md., May 1968.

6. MEETINGS:

V. Vaidhyanathan, J. R. Hamann & L. M. Bianchi participated in the 1968 N.A.S.A. Colloquium in Theoretical Biology at Michigan College, Traverse City, Michigan, July 1-31, on the "Application of Thermodynamics and Statistical Mechanics to Biology" (See also the other reports).

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

D. J. Triggle and J. R. Hamann delivered the lectures on "The Mechanisms of Receptor Action", Biophysics 509R, "Theoretical Biology", Spring Term 1968.

(See also other reports, especially from the Working Party on Symbolic Relational Systems).

8. MISCELLANEOUS ACTIVITIES:

In addition to the members' participation in committees, refereeing, etc., listed elsewhere in this report, specific refereeing in quantum pharmacology was performed for the Journ. Pharmacol. by J. R. Hamann.

# WORKING PARTY REPORT

# THEORY OF MACROMOLECULES

Acting Chairman: A. D. MacGillivray

# ANNUAL REPORT FROM WORKING PARTY ON

# THE THEORY OF MACROMOLECULES

1. DEFINITION OF FIELD OF INTEREST:

A theoretical study of the role of electrostatic free energy on macromolecule interactions in biological systems, especially the 'DNA helix-coil transition'.

2. FINANCIAL SUPPORT:

N.A.S.A. Grant No. NGR 33-015-016

N.I.H. Grant No. GM 11603

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| A. I. McMullen | Working Party Chairman Professor, Biophysics Department, School of Pharmacy (New chairman to be appointed). |
| A. D. MacGillivray (Acting Chairman) | Associate Professor Department of Mathematics. |
| R. Rein | Associate Research Professor, Biophysics Department, School of Pharmacy, and Roswell Park Memorial Institute |
| J. Marinsky | Professor, Faculty of Natural Science and Mathematics, and Department of Chemistry |
| M. Ycas | Consultant SUNY/Syracuse, Upstate Medical Center |
| N. Goel | Consultant University of Rochester |

4. RESEARCH PROGRAM:

A. Helix-coil transition and its dependence on ionic strength. For some time now Dr. McMullen and Dr. MacGillivray have been working on the calculation of the electrostatic contribution to the free energy change between "helix" and "random coils" configurations, with the intention of eventually applying our results to other macromolecules of interest, including globular proteins. It is assumed that the nonlinear Poisson-Boltzmann equation describes the physics. From a purely computational point of view, our theory is the most sophisticated one I know of. The variational principle (MacGillivray and Swift, 1968) has been successfully used to calculate the free energy using two trial functions in a semi-direct method (MacGillivray and McMullen, 1968).

Attempts to solve a more sophisticated model of DNA using three trial functions have not been successful, in spite of two years intermittent and often very determined effort. The difficulty lies in the exponential instability of the shooting method used to solve the nonlinear boundary value problem; with one function the method is fairly easy, with two functions just manageable, and with three it is at best impractical.

The shooting method is being abandoned partly for the above reason, but also partly because the degree of ion binding to use is not clear. If ion binding is as high as 78% (as used by Schildkraut and Lifson, 1965) then,

even though there may exist high potentials, the linearized Debye-Hückel approximation can be used at low and high salt (MacGillivray and Winkleman, 1966). In this situation the time-consuming effort spent on the nonlinear formulation is largely wasted. Furthermore, the solution for quite reasonable charge configurations on the DNA are relatively easy to obtain in the linearized case. This is a possible future project which can be done in collaboration with a student (see 7 below).

Even if the ion binding is so low that the Debye-Hückel approximation cannot be used, the presently used shooting method for solving the differential equations may be scrapped in favor of the method developed in project B.

B. Integral equation approach to solving Poisson-Boltzmann equation. During the summer 1968 A. D. MacGillivray developed a method for solving the Poisson-Boltzmann equation based on special iterations of the associated integral equation, and successfully applied it to the one-dimensional problem. Formally, at least, the method can be applied to the nonlinear partial differential equation. Now, Mr. Craig Spirka and I have been working on an ion exclusion problem (see Dresner, 1963, 1965, MacGillivray and Swift, 1968) and the numerical solutions needed have thus far used shooting methods, and the exponential instability has made further needed calculations very difficult (although we have only one function, not three) if not impossible. Hence, during Winter Recess,

I shall try to solve the problem by using the above mentioned iteration method.

C. Ion Exclusion Problem. As outlined under Project B, we have been studying the ion exclusion problem of Dresner (MacGillivray and Swift, 1968), and are currently continuing efforts in this direction.

D. Asymptotic Solutions of Poisson-Boltzmann Equation. A condition has been derived which assures that the Debye-Hückel solution uniformly approximates the Poisson-Boltzmann solution at low ionic strengths, (MacGillivray, 1968). The theory is applicable to several important systems.

E. Ion Transport Across Membranes Based on Nernst-Planck Equations. During the past year I was able to show that both the electro-neutrality assumption and Teorell's Donnan equilibrium assumption for membranes carrying a fixed charge can be derived from an asymptotic expansion of the solution corresponding to a "thick" membrane. (MacGillivray, 1968). Also, a first order perturbation theory for an uncharged membrane is essentially complete, and the corresponding theory for a charged membrane is under way.

Dr. Daphne Hare and I have worked out the first order perturbation theory for "thin membranes", and considered its applicability to biological systems (MacGillivray and Hare, 1968).

There are several asymptotic expansions needed to fill out the picture, the easier ones being possible future

project which can be done in collaboration with students (See 7 below).

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. MacGillivray, A. D., and McMullen, A. I., "Theory of Helix-Coil Transition Based on the Nonlinear Poisson-Boltzmann Equation". J. Theoret. Biol., 19, 1968.

2. MacGillivray, A. D., "Nernst-Planck Equations and the Electroneutrality and Donnan Equilibrium Assumptions". J. Chem. Phys., 48, 1968.

3. MacGillivray, A. D. and Swift, J. D., "On the Variational Principle for the Poisson-Boltzmann Equation", J. Phys. Chem. 72, 1968.

4. MacGillivray, A. D., "Asymptotic Solution of the Poisson=Boltzmann Equation for a Charged Sphere, and Implications", In Press, J. Theoret. Biol., 1968.

5. Submitted to J. Gen. Phys., Oct. 1968: MacGillivray, A. D. and Hare, D., "Applicability of Goldman's Constant Field Assumption to Biological Systems".

Other References

1. Schildkraut, C. and Lifson, S., Biopolymers 3 (1965)

2. MacGillivray, A. D. and Winkleman, J. J., J. Chem. Phys., 45, 1966

3. Dresner, L., J. Phys. Chem. 67 (1963), 69 (1965)

6. MEETINGS:

None

7. CONTRIBUTION TO UNIVERSITY TEACHING:

For the past couple of years I have been able to obtain good undergraduate students to work with me on meaningful problems, with the definite intention of publishing the results. J. D. Swift worked with me in this way (supported by U.H.F.) and C. Spirka is currently working with me. (Summer support from NSF). Future projects of this sort are mentioned in the above text under projects A and E.

# WORKING PARTY REPORT

# CELL MEMBRANES

Chairman J. F. Danielli

# ANNUAL REPORT FROM

# WORKING PARTY ON CELL MEMBRANES

## 1. DEFINITION OF FIELD OF INTEREST:

Theoretical and experimental work relevant to the understanding of cell membranes.

## 2. FINANCIAL SUPPORT:

Danielli, Ohki: NASA Grant NGR-33-015-016; NSG 501
NIH Grant GM-11603, NGR 33-015-002
School of Pharmacy

Papahadjopoulos: Center for Theoretical Biology
American Heart Association
GRS Grant (SUNY)

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

J. F. Danielli — Professor of Theoretical Biology, Department of Biophysics, School of Pharmacy and Biology Department, Faculty of Natural Sciences and Mathematics

D. J. Triggle — Associate Professor, Departments of Biochemical Pharmacology and Biophysics, School of Pharmacy

J. Moran — Assistant Professor, Department of Biochemistry, School of Pharmacy

S. Ohki — Assistant Professor, Biophysics Department School of Pharmacy

P. D. Papahadjopoulos - Assistant Professor, Department of Biochemistry School of Medicine

| | |
|---|---|
| J. Borst | Graduate Student, Research Assis. |
| A. Goldup | Visiting Professor,<br>Center for Theoretical Biology |
| M. H. F. Wilkins | Consultant,<br>(Professor of Biophysics,<br>King's College, London) |

4. RESEARCH PROGRAM:

Further studies have been made, particularly by S. Ohki, on the theory of Danielli that the stabilization of bilayers is attributable to a free energy minimum at the bilayer thickness. Ohki has established relationships between asymmetry of polarisability of the oriented hydrocarbon chains of phospholipid membranes, and the asymmetry of dielectric constant and refractive index of the membranes. To define the microstructure of such a membrane to a first approximation, it is necessary to know:

1) the thickness of the membrane
2) the area per hydrocarbon chain
3) the average angle between the C-C bonds in a chain and the plane of the membrane

The values for these quantities can be calculated, from measurements of:

i) the membrane capacitance
ii) the reflectance
iii) the threshold oil-water interfacial tension for penetration of a fluid droplet into the membrane

The quantities 1) to 3) above are similar to data which can be calculated from X-ray diffraction studies. Consequently studies are in progress, jointly with Wilkins group at

Kings' College, London, which will permit comparison of results obtained by the two approaches. The comparison should permit evaluation of the relevance of the model presently being used in our calculations.

Ohki has also continued his calculations of the free energy differences between bilayers, micelles and other structures, using the convention that the extra surface generated over and above that present in the bilayer is $CH_2/H_20$ interface, with a free energy of ca. 50 ergs/$cm^2$. Ohki, Goldup and Papahadjopoulos have studied the resistance and capacitance of bilayers at various pH and at various concentrations of $Na^+$, $K^+$, $Ca^{++}$ and $Mg^{++}$. Goldup has studied the permeability of these membranes to alcohols. The general picture which emerges is that the membranes are stable over a wide range of pH, including the physiological range, and the stability is increased by the presence of divalent cations. With egg lecithin conversion to micelles occurs when the net charge significantly exceeds one electronic charge per molecule of phospholipid.

Borst has made preliminary calculations on electrostatic interaction between proteins on opposite faces of the membrane. The energies of interaction may be large compared with kT, so that the presence of a given protein on one side of a membrane may determine which of a set of proteins may be selected for presence on the opposite side.

Papahadjopoulos is studying the interaction of proteins, particularly a glycoprotein from red cell membranes, with phospholipids.

Danielli has made calculations based on lipid analyses of PPLO membranes, the data for which were supplied by H. Morowitz. These calculations show that the PPLO in question could utilize fatty acids from $C_{10}$ to $C_{24}$ in chain length to obtain functional membranes, provided that the cohesion pressure between chains could be fairly close to that found for myristic acid ($C_{14}$). Thus for these cells there appears to be a requisite physical structure for the chains, but no requirement for chain length. He has also made some preliminary calculations on peptide-phospholipid interactions in bilayers. It appears that peptides e.g., cyclic peptides, can stabilize cylindrical packings of phospholipids extending through the thickness of bilayers. The interior of these cylinders are polar.

The work of Moran and Triggle is reported elsewhere. The following refer to J. F. Danielli.

5. PUBLICATIONS, PAPERS, SEMINARS:

1. Phospholipid Membranes are Necessarily Biomolecular, Mol. Assoc. in Biol., Academic Press (1968)
2. Inheritance of the "Life-Spanning" Phenomenon in Amoeba Proteus, Audrey Muggleton, J.F. Danielli, Exp. Cell Res. 49, 116-120 (1968)

6. MEETINGS:

1. Lehigh University, Seminar for Chemistry Department January 8-11.
2. Seminar in Biophysics & Medical Physics, Donner Lab., Berkeley, California, February 12-16.

3. Seminar, Milan; Paper to Society for Experimental Biology, Bristol, England, March 11-28.*

4. Lecture, New York State Section, American Physical Society, March 30.

5. C.U.E.B.S. Meeting, Washington, D.C., May 4-5.

6. Seminar to Biologists at University of Indiana, Bloomington, Sept. 3-5; and to American Chemical Society at Rochester

7. Seminar & Conference on the Physical Principles of Biological Membranes, December 17-22, Coral Gables, Florida.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

J. F. Danielli has given lectures and seminars on various occasions.

* Elected to Honorary Membership, Society for Experimental Biology.

PROGRESS REPORT - P. Demetrios Papahadjopoulos

1. DEFINITION OF FIELD OF INTEREST:

Theoretical and experimental studies of biophysical properties of phospholipids, permeability of phospholipid model membranes; interactions of phospholipids with isolated membrane proteins.

2. FINANCIAL SUPPORT:

Center for Theoretical Biology

American Heart Association

GRS Grant (SUNY)

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Assistant Research Professor at Department of Biochemistry, SUNY at Buffalo; member of C.T.B., SUNY at Buffalo; Visiting Senior Cancer Research Scientist at R.P.M.I.; established investigator of the American Heart Association.

4. RESEARCH PROGRAM:

Interaction of Red Cell membrane proteins with phospholipids: a glycoprotein isolated from erythrocyte stroma has been used to study the recombination of membrane protein with phospholipids. The solubilization and purification has been accomplished without the use of detergents which would interfere with subsequent recombination with phospholipids.

The conditions favoring the formation of a phospholipid-protein complex were investigated. The complex has been isolated by centrifugation on density gradients, and its chemistry is now being studied in terms of ratios between phospholipid/peptide/hexose/sialic acid.

Further studies on the physicochemical properties and permeability characteristics of the reconstituted phospholipid-protein complex are now in progress.

Permeability of phospholipid model membranes: previous studies on the permeability of phospholipid liquid-crystalline vesicles have now been extended to include cardiolipin, an important constituent of mitochondrial membranes.

In collaboration with Dr. S. Ohki of the Department of Biophysics, a study has been made on the effect of bivalent metals and pH on the permeability properties of phosphatidylserine bilayer membranes. A manuscript describing the results is now being prepared for publication.

5. PUBLICATIONS, PAPERS, SEMINARS:

1. Papahadjopoulos, D. "Surface Properties of Acidic Phospholipids: Interaction of Monolayers and Hydrated Liquid Crystals with Uni and Bi-valent Metal Ions", Biochim. Biophys. Acta., 163,240, 1968

2. Bennett, P.B., Papahadjopoulos, D., and Bangham, A.D. "The Effect of Raised Pressure of Inert Gases on Phospholipid Membranes", Life Sciences, 6, 2527, 1967.

6. MEETINGS:

1. "Structural Characteristics and Permeability Properties of Hydrated Liquid Crystals Derived from Phospholipids", Gordon Conference on Interaction and Transport, June, 1968, Tilton, N.H.
2. "Structural Characteristics and Permeability Properties of Liquid Crystalline Phospholipid Vesicles", conference on Cold Adaptation, Membranes and Lipid Metabolism. Sponsored by Institute of Artic Biology and American Institute of Biol. Sciences, Fairbanks, Alaska, July, 1968, Fairbanks.
3. "Surface Properties and Permeability Characteristics of Acidic Phospholipids: Interaction of Monolayers and Hydrated Liquid Crystals with Bivalent Metal Ions", Symposium on Stability of Thin Films, American Chemical Society Meeting, September, 1968, Atlantic City, N.J.
4. Seminar at the Experimental Biology Department at Roswell Park Memorial Institute, December 5,1967.
5. Lecture at the Department of Biochemistry, University of Toronto, February 5, 1968.
6. Seminar at the Bunting and Best Institute for Medical Research, University of Toronto, November 1, 1968

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

Participation in the following courses during

Fall semester 1968:

501 Biochemistry for Medical Students

605 Energy metabolism (Four lectures on biological membrane structure and function.)

PROGRESS REPORT - S. Ohki

1. DEFINITION OF FIELD OF INTEREST:

Theoretical and experimental studies of phospholipid bilayers and biological membranes.

2. FINANCIAL SUPPORT:

NASA Grant NGR 33-015-016

NIH Grant GM 11603

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Assistant Professor, Department of Biophysics, State University of New York at Buffalo.

4. RESEARCH PROGRAM:

5. PUBLICATIONS, PAPERS, SEMINARS:

1. Ohki, S. and Fukuda, N. "Interaction Energy Between Water and Hydrocarbon Phases", J. Colloid and Interface Sci. 27, 208 (1968a)

2. Ohki, S. "Dielectric Constant and Refractive Index of a Lipid Bilayer", J. Theoret. Biol. 19,97,(1968b)

3. Ohki, S., Goldup, A. "Influence of pH, Sodium and Calcium Ions on the D.C. Resistance of Black Egg Lecithin Cholesterol Films",Nature 217, 459 (1968)

6. MEETINGS:

1. Ohki, S. and Goldup A. "Influence of pH, Sodium and Calcium Ions on the D.C. Resistance of a Lipid Bilayer", Biophysical Society Twelfth Annual Meeting, Pittsburgh, Penna., February.
2. Ohki, S., "Lipid Bilayer-Micelle Transformation", 156th National ACS Meeting, Atlantic City, N.J., September

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

Participation in the following courses:
Biophysics 511 (Laboratory Course)
Biophys 689-690 (Research Course)

## PROGRESS REPORT - J. F. Moran

1. DEFINITION OF FIELD OF INTEREST:

Interactions of neurotransmitters (Norepinephrine and Acetylcholine) with their corresponding receptors and the relationship of this interaction to the subsequent physiological and biochemical responses.

2. FINANCIAL SUPPORT:

NIH

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Assistant Professor, Department of Biochemistry, Schools of Medicine, Dentistry and Pharmacy

4. RESEARCH PROGRAM:

(See report of Working Party on Receptor Structure)

5. PUBLICATIONS, PAPERS, SEMINARS:

1. "A Further Investigation of the Spare Receptor Hypothesis and the Mechanism of Action of 2-Halogenoethylamines",J. F. Moran, C. R. Triggle and D. J. Triggle, J. Pharm. Pharmacol. 20 (1968)
2. "Receptor Isolation and Quantitation", J. F. Moran, D. J. Triggle presented at the Third Annual Symposium on Molecular Pharmacology, Buffalo, N.Y., August.
3. "Acetylcholine Receptor - An Allosteric Mechanism for Inhibition", Seminar in Department of Biochemistry, November.
4. American Chemical Society Meeting, San Francisco, California, April.

6. MEETINGS:

Chairman, Sub-committee on allocations, United Health Foundation Consultant, Panel on Mental Health and

Retardation, United Health Foundation.

7. CONTRIBUTION TO UNIVERSITY TEACHING:

Medical, Dental and Pharmacy student biochemistry laboratory; eight lectures in a graduate course in Biochemistry BC 601, and a joint course with D. J. Triggle entitled: "Molecular Basis for Chemical Transmission Processes", BP 630, 630R; BC 630, 630R).

# WORKING PARTY REPORT

# QUANTUM BIOCHEMISTRY

Chairman: R. Rein

ANNUAL REPORT FROM WORKING PARTY ON QUANTUM BIOCHEMISTRY

1. DEFINITION OF FIELD OF INTEREST:

The general field of interest of this research effort is the application of quantum mechanical and related techniques to biologically important molecules (bio-molecules) and the interpretation and correlation of such calculations with regards to molecular stability and interactions. Such information will allow biological inferences to be made.

2. FINANCIAL SUPPORT:

Research activities of the group were supported mainly by the respective departments of the members. A particularly important role was played by the Department of Experimental Pathology of Roswell Park Memorial Institute. Further support was received from Roswell Park Memorial Institute through Graduate School training N.I.H. Grant No. CA-5016-12.

Additional support was received from N.I.H. Grant No. 213002 through SUNY Computer Center, in the form of free computer time. The Center for Theoretical Biology supported the work of this group through its facilities and supporting personnel, as well as through N.A.S.A. Grant No. 33-015-016, and N.I.H. Grant No. GM 11603.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| Dr. Robert Rein | Chairman<br>Principle Cancer Research Scientist, Dept. Expt. Pathology and Biophysics, Roswell Park Memorial Institute. |
| Dr. Michael Pollak | Associate Professor of Physics, University of California at Riverside, Visiting Professor, C.T.B. |
| Dr. Frank E. Harris | Professor of Physics<br>University of Utah |
| Dr. George A. Clarke | Assistant Professor of Chemistry, SUNY/Buffalo |
| Dr. James P. Harlos | Cancer Research Scientist Dept. Experimental Pathology, Roswell Park Memorial Institute. |
| Dr. Sasa Svetina | Cancer Research Scientist Dept. Experimental Pathology, Roswell Park Memorial Institute |
| Dr. Mordechai Kleiner | Cancer Research Scientist Dept. Experimental Pathology, Roswell Park Memorial Institute |

Graduate Students:

| | |
|---|---|
| Mr. James Rabinowitz | Physics Dept., Roswell Park Memorial Institute |
| Mr. Robert Sayre | Biophysics Dept.<br>SUNY/Buffalo |
| Mr. George Pack | Biophysics Dept., Roswell Park Memorial Institute |
| Mr. Joseph Smith | Physics Dept., University of California, Riverside (visiting C.T.B.) |

Computer Programmers:

| | |
|---|---|
| Mr. Ehud Artzy | Roswell Park Memorial Inst. |
| Mr. Dennis DeGweck | C.T.B., SUNY/Buffalo |
| Miss Hsin-yu Wang | C.T.B., SUNY/Buffalo |
| Mr. Joseph Lampel | C.T.B., SUNY/Buffalo |

Scientists visiting during the year:

| | |
|---|---|
| Dr. Daniel Fiat | Weizmann Institute of Science Rehovoth, Israel |
| Dr. Joost Manassen | Weizmann Institute of Science Rehovoth, Israel |
| Dr. Petr Hochmann | Institute of Physical Chemistry, Czechoslovak Academy of Sciences, Prague, Czechoslovakia |

4. RESEARCH PROGRAM:

This research effort is concerned with a manifold of programs relating to the use of quantum mechanics and other theoretical approaches in molecular biology. Our primary goal is the ability to evaluate and interpret biomolecular behavior and interactions in a reasonably exact manner. Therefore, a considerable amount of the current research has been spent in refining and improving present methods of calculation.

A major difficulty of semi-empirical techniques, such as those previously used, is the estimation of parametric values of the various electronic integrals. To eliminate this problem we have been concerned with a

two-fold attack on the rapid evaluation of the multi-centered electron repulsion integrals. The first method is an exact evaluation of these integrals using analytical rather than numerical computational techniques. This has led to the development of the required master formulae. The second method is concerned with approximating these integrals by application of a variational technique to single center expansions of charge distributions. Preliminary calculations using this technique have been favorable.

Another major area of our interests is involved with the problem of molecular interactions. To this end we are examining the use of ground state properties in perturbation techniques such as Salem's method, for computing the energies involved in photo dimerization and interaction of bio-molecules.

On another level this area also includes the extension and refinement of previously described methods of calculating molecular interaction to incorporate, in a more exact manner, the effects of the overlap of the electronic wave function of the interacting molecules. Such calculation will allow comparison with a variety of experimental data, such as the hypochromic shift of biopolymers.

Research Reports Appended

| | | |
|---|---|---|
| 1. | Integral Approximation | R. Rein, J. Rabinowitz, J. Harlos, S. Svetina, D. DeGweck |
| 2. | Multi-Center Integral Evaluation | F. E. Harris, R. Rein J. Harlos |
| 3. | General Theory of Intermolecular Interactions | M. Pollak, J. Smith, R. Rein |
| 4. | Method for Calculating Intermolecular Interaction Energies | R. Rein, J. Smith, J. Harlos, R. Sayre |
| 5) | Quantum Chemistry of Thymine Photo Dimerization | R. Rein, R. Sayre, J. Smith, J. Harlos, M. Pollak |
| 6) | Quantum Chemistry of Urocanic Acid Photo Dimerization | R. Sayre, J. Smith, J. Harlos, R. Rein |

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Molecular Orbital Study of the Hydrogen Bonding of Water", Rein, R., Clarke, G. A. and Harris, F. E., J. of Molecular Structure 2, 103 (1968)
2. "A Semi-Empirical Analysis of the Melting Curves of Synthetic DNA Molecules and the Calculation of the Stacking and Pairing Energies and Entropies in DNA", Goel, N., Fukuda, N., and Rein, R.
3. "Iterative Extended Hückel Study of Nucleic Acid Bases", Rein, R., Fukuda, N., Clarke, G. A. and Harris, F. E., J. of Theor. Biology, 21, 88-96 (1968)

4. "An Examination of the Energetics of Crick's Wobble Hypotehsis", Pollak, M. and Rein, R., J. of Theor. Biology, 19, 241 (1968)

5. "An Electrical Mechanism for Strand Separation in DNA", J. of Theor. Biology, 19, 333 (1968)

6. "Quantum Mechanics in Biochemistry", Rein, R., and Harris, F. E., In Press, Encyclopaedic Dictionary of Physics.

7. "On the Calculation of London-Van der Waals Interactions in a Monopole-Bond Polarizability Approximation with Application to Interaction Between Purine and Pyrimidine Bases", Rein, R., Claverie, P., and Pollak, M., Int. J. of Quantum Chemistry, Vol. II, 129-144 (1968).

6. MEETINGS:

Dr. Rein presented papers at the following meetings:

1. International Symposium on Atomic, Molecular and Solid-State Theory and Quantum Biology, Sanibel Island, Fla.

   Presented paper:

   "Survey of Quantum Biological Research in Buffalo", R. Rein.

2. 12th Annual Meeting of the Biophysical Society, Pittsburgh, Pa.

Presented papers:

a) "On Stability of Crick's Wobble Pairs", M. Pollak and R. Rein.

b) "Comparative Study of Total Valence Electron in Molecular Orbital Models - Application of the Nucleotide Bases - Water and Water Dimers", R. Rein, N. Fukuda, G. A. Clarke, J. Hamann and F. E. Harris

c) "Studies of the Electronic Structure of Amino Acids and Peptides by Means of the Iterative Extended Huckel Theory", R. Rein and P. Cota.

3. American Chemical Society 155th meeting, San Francisco, Calif.

Presented paper:

"Comparative Studies of the Nucleic Acid Bases", R. Rein, N. Fukuda, G. A. Clarke, J. Hamann and F. E. Harris.

4. International Biophysics Symposium on Membrane Permeability, Jerusalem, June 1968

V. S. Vaidhyanathan paper presented by R. Rein.

7, CONTRIBUTION TO UNIVERSITY TEACHING:

The educational activities include a course in Quantum Biophysics (348) presented by Dr. R. Rein. The course was oriented to provide a fundamental understanding

of the principles of quantum mechanics with regards to molecular and biological process.

The course was designed to provide the fundamental mathematical background necessary to comprehend and apply the results and methods of quantum mechanics. This included an introduction also of the methods of group theory as related to quantum mechanical problems.

The educational activities of the quantum biology group also incorporate a research oriented course in molecular quantum mechanics conducted by Dr. Robert Rein with the assistance of Dr. J. Harlos. The philosophy and objectives of this course is to present a self-consistent development of the quantum mechanical treatment of molecules allowing the students to develop a familiarity with present techniques. This familiarity is given a firm practical base by the inclusion of a "laboratory section" where molecular orbital programs are written and used for the calculation of molecular parameters. Our objective, therefore, is to provide the student with sufficient theoretical background to understand current research and to be able to apply the theory to any particular research problem and to provide sufficient practical understanding and practice in the computational methods and techniques to make such application possible.

The research training course is conducted, at present, in an informal manner and meets once a week for approximately three hours, It is limited to ten participants, including Drs. Rein and Harlos. The topics covered, to the present time, include: an introduction to many bodied theory with the development of the many electron hamiltonian, the Born-Oppenheimer approximation and product wave function, introduction to the evaluation of expectation values of observables, development of pi-electron Hückel-Molecular Orbital theory and computer program, the theory and use of antisymmetrized product wave functions, the formulation of the Hartree-Fock equations and the development of the Parier-Parr-Pople method for pi-electron systems. These topics, of course, only sketch out the highlights of the course and do not explicitly include the detailed mathematical or practical developments included in the course. The course will continue with the development of better approximating techniques to allow calculations on molecular systems utilizing valence shell, and total electron methods and the use of M.O. theories in evaluating or interpreting problems of interest in theoretical biology.

At present research activities include studies in photo dimerization using Salem's perturbation techniques, the development of a CNOO program for closed and open shells for an examination of chemical reactivity and ESR studies of biological molecules.

8. MISCELLANEOUS ACTIVITIES: R. Rein

1. Member of the Academic Committee of the Center for Theoretical Biology
2. Presented invited seminars at:
   a) Stanford University, Paolo Alto, Calif.
   b) NASA Ames Research Center, Moffett Field, Calif.
3. Visited and presented a course of 30 lectures on selected topics on Quantum Chemistry at Weizmann Institute of Science, Rehovoth, Israel.
4. Refereeing for Journal of Theoretical Biology and the Biophysical Journal.

## 9. APPENDIX:

### Integral Approximation

The rigorous quantum mechanical treatment of medium to large molecules, in particular those of biological significance, is limited primarily by practical considerations. Foremost of these is the time required for the evaluation of the large number of integrals arising in self-consistent field calculations. These range in difficulty from the rather simple single center integrals to the difficult three and four center integrals.

In general one solves these multi-centered integrals by reducing them to a sum of one and two center integrals. We are approaching this problem in two ways; one is the development of exact analytical formulations for these integrals and is described elsewhere; the other method is concern with developing mathematical approximations for two center charge distributions, $\Omega ab$, defined by

$\Omega ab = \psi_a(1)\ \psi_b(1)$ where $\psi_a$ and $\psi_b$ are Slater type orbitals (STO) located at centers "a" and "b". The multicenter electron repulsion integrals can then be expressed as,

$$\int \psi_a^*(1)\ \psi_b(1)\ r_{12}^{-1} \psi_c^*(2)\ \psi_d(2)\ d_{\tau_1}\ d_{\tau_2} = [\Omega ab | \Omega cd]$$

We have shown previously that an optimal method of treating these two center charge distributions requires the expansion of the STO located on one center in terms of symmetry limited STO's on the other center. Our present treatment is an extension of the basic concepts

contained in the previous treatment. It will be noted that the given orbital expansion results in the two center charge distribution ($\Omega ab$) being given as a sum of one center charge distributions. The present treatment makes use of this observation and expands $\Omega ab$ in terms of basic one center charge distributions, vz,

$$\Omega ab = \sum_i C_i \, e^{-\delta_i r} \, r^{(n_1+n_2-1)-1} \, Y_{\ell_1 m_1} Y_{\ell_2 m_2}$$

where $n_1$ $n_2$ $\ell_1$ $\ell_2$ $m_1$ $m_2$ are the quantum numbers associated with the distribution $\Omega ab$ and $Y_{\ell m}$ is a spherical harmonic. The $C_i$ and $\delta_i$ are adjustable parameters and the summation is, in general, limited to two terms per center.

The adjustable parameters, C and $\delta$ are at present determined using variational methods and use at least squares fit to the exact form of the charge distribution $\Omega ab$, i.e. we vary all of these C's and $\delta$'s as independent parameters to minimize the square of the difference between the function approximated and the approximating function. Alternate procedures based on the conservation of certain moments of charge will also be examined. At present the $\delta$ parameters are evaluated using a steepest desents technique while the C parameters are minimized by conventional linear techniques. The possibility that similar treatments for both the C's and $\delta$'s may be a more optimal method is also being examined.

The calculations described above have been programmed for all the limited basic set usually considered in Hartree-Fock calculations.

Preliminary calculations indicated that the approximate values for integrals lie within 6% of the exact values.

R. Rein, J. Rabinowitz, S. Svetina, J. Harlos, D. DeGweck

## Multi-Center Integral Evaluation

The application of quantum mechanics, in forms other than semi-empirical molecular orbital approximations, to molecules of chemical or biological interest presents many formidable computational problems. Foremost of these is the rapid, accurate evaluation of multi-centered integrals. These integrals are usually evaluated by expanding the orbitals involved about some arbitrary point and reducing the integral to a sum of one and two center integrals. These resulting integrals can be evaluated by many techniques, with numerical integration being typically used. The present discussion covers work dealing with the development of analytical solutions for the evaluation of multicentered integrals. Approximate solutions of this problem are discussed in another section.

We define the multicentered integral to be of the form

$$[\psi_a\psi_b|\psi_c\psi_d] \equiv \int\int \psi_a^*(1)\ \psi_c^*(2)\ r_{12}^{-1}\psi_b(1)\ \psi_d(2)\ d_{\tau_1}\ d_{\tau_2} \qquad (1)$$

where the orbitals $\psi_a$ are Slater type orbitals located at centers a, b, c and d (in general these are different). The location of the atom centers can be given by the set of polar coordinates Ra, θa, ζa which are measured from some origin. The electrons however are located with respect to the atom centers. Each of these orbitals may be expanded about some arbitrary point, say the origin. The formulation of this expansion has been shown to be,

$$\psi_a(1) = \sum_{\mu=0}^{\infty} \sum_{\sigma=-\mu}^{+\mu} \sum_{\lambda=|\ell-\mu|}^{\ell+\mu} \left(\frac{2\mu+1}{4\pi}\right)^{1/2} C_{\lambda\ \mu\ \ell}^{m+\sigma,\sigma,m}\, Y_{\lambda,m+\sigma}(\Omega_A)\, Y_{\mu,\sigma}(\Omega_A)$$

$$V_{\mu\lambda\ell}(r_1, R_A) \qquad (2)$$

where $C_{\lambda\ \mu\ \ell}^{m+\sigma,\sigma,m}$ are Clebsh-Gordon coefficients, the Y's are spherical harmonics with arguements Ω; $\Omega_A$ represents the angular spherical coordinates $(\theta_A, \zeta_A)$ locating the atom center and $\Omega_1$ those of the electron relative to the expansion center. The $V_{\mu\lambda\ell}(r_1, R_A)$ are the radial parts of the expanded wave function, where $r_1$ and $R_A$ are the electron and atom center distances measured from the expansion center.

With similar expansions for the remaining orbitals, the usual Laplace expansion for $r_{12}^{-1}$ and integration over the angular electron coordinates one obtains the expression

$$[\psi_a\psi_b|\psi_c\psi_d] = \sum_{(\mu)} \sum_{(\lambda)} \sum_{\rho} (2\rho+1)^{-1} A^{\rho}_{(\mu)(\lambda)} \int_0^{\infty} r_1^2 dr_1 \cdot \int_0^{\infty} r_2^2 dr_2 \ \frac{r_1^{\rho}}{r_2^{\rho+2}} \ V_{\mu\lambda}(r_1 R_A) \cdot V_{\mu'\lambda'}(r_1 R_B) \ V_{\mu''\lambda''}(r_2 R_C) \ V_{\mu'''\lambda'''}(r_2 R_D) \qquad (3)$$

where $(\mu)$ and $(\lambda)$ represent $\mu$, $\mu'$, $\mu''$, $\mu'''$ and $\lambda$, $\lambda'$, $\lambda''$, $\lambda'''$ respectively, and $A^{\rho}_{(\mu)(\lambda)}$ incorporates the angular part of the wave function. According to Harris and Michaels (J. Chem. Phys., 45, 116 (1966) equation (3) can be transformed to eliminate the $r_{<}^{\rho}/r_{+}^{\rho+1}$ factor giving:

$$[\psi_a\psi_b|\psi_c\psi_d] = \sum_{(\mu)}\sum_{(\lambda)}\sum_{\rho} A^{\rho}_{(\mu)(\lambda)} \int_0^{\infty} dz z^{-2\rho+2} \int_0^{z} dx\, V_{\mu\lambda\ell}(x_1 R_A)\, V_{\mu'\lambda'\ell'}(x\, R_B) \cdot \int_0^{\infty} d\, V_{\mu''\lambda''\ell''}(y\, R_C)\, V_{\mu'''\lambda'''\ell'''}(y\, R_D) \qquad (4)$$

The $V_{\mu\lambda\ell}(rR)$ are now defined, according to Silverstone, (J. Chem. Phys. 47, 537 (1967) for STO's with principle quantum number "n" and screening parameter as,

$$V_{\mu\lambda\ell}(rR) = 4\pi \left(-\frac{d}{d\xi}\right)^{n-\ell}\left(\frac{1}{\xi}\frac{d}{d\xi}\right)^{\ell}\xi^{\ell+1} V_{\mu\lambda}(rR) \qquad (5)$$

with

$$V_{\mu\lambda}(r_1 R) = K_{\lambda}(\xi R)\, I_{\mu}(\xi r) \qquad r < R$$

$$V_{\mu\lambda}(r_1 R) = (-1)^{\mu+\lambda} I_{\lambda}(\xi R)\, K_{\mu}(\xi r) \qquad r > R \qquad (6a)$$

where $K_{\lambda}(x)$ and $I_{\mu}(x)$ are modified spherical Bessel functions,

$$I_{\mu}(x) = x^{\mu}\left(\frac{1}{x}\frac{d}{dx}\right)^{\mu} I_0(x)$$

$$I_0(x) = x^{-1}\sinh x$$

$$K_{\lambda}(x) = x^{\lambda}\left(-\frac{1}{x}\frac{d}{dx}\right)^{\lambda} K_0(x)$$

$$K_0(x) = x^{-1} e^{-x} \qquad (6b)$$

Due to the two-region character of $V_{\mu\lambda}(rR)$ expressed by equation (6a) the integral given in equation 4 can be naturally partitioned according to the relative magnitudes of x and y with respect to $R_a$, $R_b$, $R_c$ and $R_d$. It has been shows in the present study that such partitioning allows the integral to be expressed as a sum of single-region integrals. Furthermore, these single region integrals are expressable in terms of a exponential integral, $A_n(x)$ and a new function $F_{\mu\nu}(\alpha\beta)$, defined as

$$F_{\mu\nu}(\alpha\beta) = \int_1^\infty z^\mu A_\nu(\beta z)\, e^{-\alpha z} dz \qquad \alpha > 0 \tag{7}$$

Since both of these functions can be recursively generated the method is suitable for analytic computer solution.

Therefore, master formulae and the required computational procedures are being developed and programmed. Furthermore, such programs allowing the computation of the general 4 center integral will also allow the calculation of integrals involving smaller numbers of centers.

It is hoped that this type of analytic formulation of these integrals will allow for more rigorous molecular orbital calculations of at least medium sized ($\sim$ 20 atoms) biologically important molecules. Such calculations would provide much information concerning interaction sites, energies of activation and other related information.

F. E. Harris, R. Rein and J. Harlos

General Theory of Intermolecular Interactions

The methods for calculating intermolecular interactions which we developed a few years ago have been applied to a number of systems. Perhaps most interesting from the biological point of view was the possibility to utilize this method to examine the feasibility of Crick's wobble hypothesis from the point of view of energetic stability. Other applications were relevant to the thermal denaturation of DNA, a possibility for electrical denaturation of DNA, which we proposed, the stability of the replication plane of DNA proposed by Löwdin, and the hydrogen bonding systems between purines and pyrimidines. While at first our method had only the capability to evaluate the interaction energy due to the $\pi$ electron system our latest method could, to some degree, also include the $\sigma$ electron system. An additional improvement was the extension of the capability to compute the interaction energy for a specified configuration to the capability to determine automatically the configuration with the largest attractive interaction energy. Although our applications so far were very satisfactory insofar that they could qualitatively answer biologically significant questions, the method could not be tested on a quantitative basis because of the absence of relevant quantitative experimental data. In searching for a phenomenon which would provide an experimental standard for comparison, we found that the hypochromic effect in biopolymers seems to be almos ideally suited for this purpose. This effect

depends on precisely the same quantum mechanical entities as do the intermolecular interactions. If we can, therefore, construct a theory of the hypochromic effect which would be in quantitative agreement with a variety of experiments, we could gain great confidence in our calculations of the intermolecular interactions.

With such a goal in mind, we have undertaken to improve the methods of calculation of intermolecular interaction energies to more precisely and consistently take account of the overlap between electronic wave functions of the interacting molecules. So far we were able to construct an exact master equation for the interaction energy between molecules. While for practical reasons (amount of algebra, computer time) it is not feasible to utilize these equations in full for computational purposes, the exact equation can be conveniently reduced to approximate forms by use of different approximations as may be suitable for various practical cases. It is, for example, possible to reduce these equations into the ones commonly used with the partitioning technique, variational perturbation methods and the Rayleigh-Schrödinger perturbation method. It is also possible to see exactly what the approximations on the interacting systems are which characterize such standard approximate methods. Possible inconsistencies which such approximations may introduce in some specific cases of interacting systems are also brought out.

Going over to the more practical aspects, expressions for thevarious quantities in the master equation are now being developed. Specific attention is being paid to the programability of these expressions for computer use. The various approximations which must be made in various cases to lend practical value to the master equation are reflected both in the algebra, and in the logical setup of the computer program. For example, the algebra depends on the form in which the wave functions of the noninteracting molecules are known (closed shell, open shell, configuration interaction, etc.) The logical setup of the program is, for example, involved in the question whether the computation must be iterated or not. We plan to come up with a computer program of maximum flexibility, which will be able to perform the computations with different possible approximations.

M. Pollak, J. Smith and R. Rein

## Method for Calculating Intermolecular Interaction Energies Including Overlap and Excited State Interactions

We have for the last several years performed calculations on the interaction energies between molecules of biological interest. A number of such studies have produced figures on such biologically important phenomena as DNA melting, stacking interactions, and hydrogen bonding. The theory (Rein, Claverie and Pollak, Int. J. Qm. Chem. (1968)) treated in general the electrostatic polarization, dispersion, and exchange energies from sigma and pi

electrons of molecules, but as they were calculated assuming an intermolecular separation of 3 to 4 angstroms, overlap energies were for the most part neglected. Inclusion of overlap energies would be of particular significance in describing the dimerization and photo-dimerization of conjugated molecules and predicting the resulting dimer bond lengths. A study of those molecules of biological importance as thymine or adenine might yield significant information concerning the configuration and chemistry of DNA.

Our recent efforts for calculating intermolecular energies include both the electrostatic polarization, dispersion, and exchange energies with the overlap energies, which contribute significantly as the molecules approach one another. This method, which takes into account both ground-ground state and ground-excited state interactions of the two conjugated molecules, is adapted from the perturbation procedure developed by Salem (J. Am. Chem. Soc. (1968)). Briefly, the method calculates molecular orbital energy of interaction as a function of the atomic overlap and average effective atomic interaction energies of the atoms 2p orbitals, which are assumed to be roughly proportional to the overlap.

Preliminary studies on molecules ranging from butadiene to thymine have yielded very plausible values for the energy minima and intermolecular separation in the overlap interaction. We are currently investigating the photo-

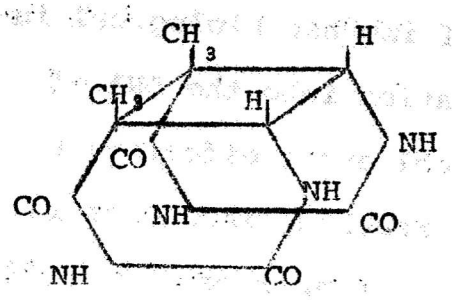
dimerization of both thymine and urocanic acid by the methods explained above and thus contribute to the elucidation of these biologically significant photodimerization reactions.

R. Rein, J. Smith, J. Harlos, R. Sayre

The Quantum Chemistry of Thymine Photodimerization

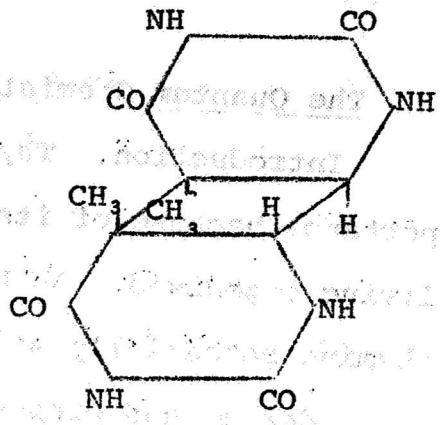
Introduction. Thymine is of immense biological importance because of its incorporation into the DNA of living organisms. An Photochemical event effecting the thymine potentially may have far reaching influence in the life, death, and propogation of the viable cell or cell system. The photochemistry of thymine involves the formation of thymine photo-hydrates, thymine dimers, and the photolysis of the dimers. Such events have been shown to occur in both in vivo and in vitro with the thymine either incorporated in DNA or free in solution. Below our discussion we will examine only such salient features of the formation of thymine dimers that effect the quantum chemical events that lead to dimerization.

Thymine Dimerization. Thymine dimers have been formed in frozen agueous solution, solutions and glasses, and in cellular DNA. Several isomeric forms have been isolated depending upon the experimental conditions (See Figure 1).



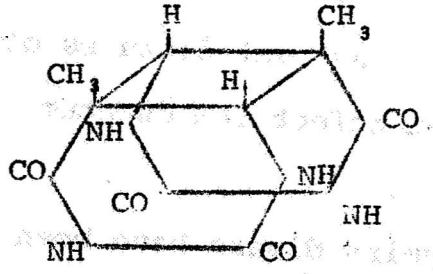

(meso)

I



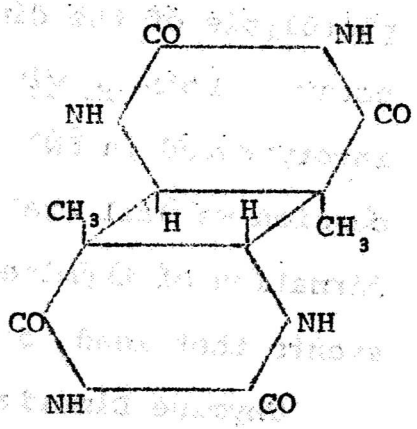

(d,ℓ)

II




(d,ℓ)

III




(meso)

IV

Fig. 1. The four cis-fused cyclobutane dimers of thymine. I (cis head-to-head), II (trans head-to-head), III (cis head-to-tail), IV (trans head-to-tail).

The current view of the mechanism for thymine dimerization requires the two thymine monomers to be in the appropriate geometrical relation. This view postulated first the excitation of one of the thymine monomers to an excited state (either a singlet or triplet state), then the formation of an excimer which through internal conversion converts to the stable configuration of the ground state dimer. Such a mechanism might involve the following steps:

$$T \overset{h\nu}{\rightleftarrows} T^1 \qquad (1)$$

$$T^1 + T \rightleftarrows \widehat{TT}^1 \qquad (2)$$

$$\widehat{TT}^1 \rightarrow \widehat{TT} \qquad (3)$$

Where T is the ground state of the thymine monomer.

$T^1$ is the first excited singlet for the thymine monomer.

$\widehat{TT}^1$ is the excited excimer singlet.

$\widehat{TT}$ is the thymine dimer ground state.

Or this reaction mechanism could involve a triplet state intermediate:

$$T \overset{h\nu}{\rightleftarrows} T^1 \qquad (4)$$

$$T^1 \rightarrow T^3 \qquad (5)$$

$$T^3 + T \rightleftarrows \widehat{TT}^3 \qquad (6)$$

$$\widehat{TT}^3 \rightarrow \widehat{TT} \qquad (7)$$

$T^3$ is the thymine triplet state.

$\widehat{TT}^3$ is the excited excimer triplet state.

The possible triplet pathway for the dimerization reaction may be of great significance in the explanation

of sensitization and quenching experiments. The mechanism for sensitized dimer formation may involve such a sequence of events as follows:

$$S \overset{h\nu}{\rightleftarrows} S^1 \qquad (8)$$

$$S^1 \rightarrow S^3 \qquad (9)$$

$$S^3 + T \rightarrow T^3 + S \qquad (10)$$

$$T^3 + T \rightleftarrows TT^3 \qquad (11)$$

$$TT^3 \rightarrow TT \qquad (12)$$

S is the sensitizer ground state

$S^1$ is the sensitizer excited to its first singlet state

$S^3$ is the lowest excited triplet state for the sensitizer.

As can be readily seen the mechanisms shown above all require that first one thymine monomer is excited to either its first singlet or triplet level, then during the lifetime of this excited molecule it reacts with a neighboring thymine to form the excited dimer which then through internal conversion now returned to the ground state of the dimer.

We are in the process of examining, using quantum mechanical methods, the energetics of these mechanisms. In particular, two steps are of immediate interest, these are the interaction of excited thymine with thymine in the ground state with the formation of an excited thymine dimer and the decay of the excited thymine dimer to its ground state. The theoretical problem inherent in

the treatment of these mechanisms are non-trivial, however, by utilizing extensively the known experimental details of the dimerization process and a constrained theoretical approach, the problem becomes tractable.

An examination of the mechanism step involving an excited thymine (in either its singlet or triplet configuration) interacting with thymine in the ground state to give rise to the excited thymine dimer, indicates that this may be envisioned, for discussion purposes, as occurring in two steps. The first step is the interaction of an excited thymine molecule with the ground state thymine molecule. At relatively long intermolecular distances this interaction may be treated by perturbation techniques. In particular, one such as described in the section dealing with Intermolecular Interaction Energies, modified to exclude the effects of electrostatic, sigma dispenses and polarization interaction. Such calculations are useful in many ways, for example they would provide information on the energy considerations of the relative orientation of the two thymine molecules and insight on the importance of these long range interactions on the distribution of dimer isomers. Such calculations also can be reduced to ground and excited state interaction energies allowing the evolution of the barrier with the ground state to dimer formation.

As the intermolecular distance approximates that of the bonding distance, extensive electronic rearrangement

occurs which is no longer treatable, in an exact fashion by perturbation techniques. However, our previous studies on total electron calculation indicates that we will be able to examine this critical region of the energy curve in a reasonably exact manner. For example, our previous work indicates that the wave function obtained in the iterative extended Hückel theory method are reasonably good and are better than the energies obtained in that method. Therefore a modified calculation of the energies using IEHT wave functions should provide the required energies.

The above treatment will provide wave functions, energies and relative electronic distribution. This information will allow us to examine such topics as the transition probabilities of the thymine dimer decay, isomer distributions and the kinetic processes involved. Such a treatment is of course not limited to thymine interaction but is equally applicable to other photodimerization process.

R. Rein, R. Sayre, J. Smith, J. Harlos and M. Pollak

## The Quantum Chemistry of Urocanic Acid Photodimerization

Introduction. Urocanic acid (UCA) is the end product of normal histidine deamination occurring in the human skin. Because of the large quantity of UCA available in the outer layers of skin together with its very extinction coefficient (UCA contributes 50 percent of the total uv absorption in the acid soluble fraction of the epidermis

and has an molar extinction coefficient of 18,000 at 265 nm), it was felt that it must play a significant role in protecting the viable layers of skin from harmful radiation. While it might contribute harmful photoproducts, no evidence has been found yet that any of its photoproducts are carcinogenic.

The Photochemistry of Urocanic Acid. a) Isomerization. In both in vivo and in vitro urocanic acid isomerizes from the normally occurring transform to a cis configuration. This reaction occurs with irradiation by sun lamps either in solution or in vivo. b) Dimerization. Dimerization occurs in both frozen aqueous solutions (analogous to dimerization of thymine) and in vivo across the ethylenic double bonds on adjacent urocanic acid molecules (Anglin and Everch, BBA 88 (1969) 492). These photodimers have been identified using paper chromotraphy, infrared and ultraviolet spectroscopy, ozone degragation and nuclear magnetic resonance. Apparently an isomorphous series of dimers result in either in vivo or in vitro formation. However by varying the pH of the frozen aqueous solution, two photo dimers occur in different amounts. As in thymine dimer formation, dimers are not formed by irradiation of dry UCA. The metabolic fate of each of these dimers have been studied, and one has been shown to be metabolically degraded in the liver, while for the other no metabolic pathway is known. c) Photoreversal of dimerization. If an aqueous solution of dimers is prepared, and the solution irradiated with short wavelength uv (254 nm)

shorter than the wavelengths that cause dimerization, the photo dimer splits again into approximately two urocanic acid monomers.

The photochemistry of UCA is seen from the above description to be quite analogous to that of thymine. The exceptions to this correlation is that for thymine photo hydrate formation occurs, and the dimer formation has been shown to be sensitized by acetophenone, which has not been demonstrated for UCA dimer formation. However, because the general conditions for dimerization of thymine and urocanic acid are so similar, one must conclude that similar quantum chemistry applies.

The Quantum Chemical Description of Dimerization. Our investigation of the quantum chemical events leading to photodimerization of urocanic acid involve a study of the energetics for the reactions between urocanic acid molecules in different configurations and at different distances of separation. We are investigating the geometries of dimers known to occur compared to the geometry of crystalline urocanic acid from which dimers are known not to occur.

This study of dimerization of UCA involves the interaction of excited state wavefunction with the ground state wavefunctions of a second molecule. The procedure that we are using is identical to that which we have developed for the study of thymine dimerization. The procedure is adapted from the perturbation treatment for cycloaddition reactions developed by Salem (J. Am. Chem. Soc. 90 (1965)

593) for hydrocarbons. However, Salem made no attempt to treat the interaction of charged groups and sigma electrons in his calculation, and any attempt to treat dimerization of urocanic acid must necessarily involve these interactions. For the terms contributed by the interaction of polarized structures, we have used the procedure developed by us (Rein, Claverie and Pollak) (J. Int. Qm. Chem., II (1968) 129), which takes into account the sigma dispersion and polarizability. The perturbation treatment appears appropriate to study the formation of the excited dimer, which occurs at a distance of around 2.5 angstroms. But as the excited dimer, through internal conversion, turns to a stable cyclobutane configuration (at 1.2 to 1.4 Å separation) through the formation of stable covalent bonds with rearrangement and rehybridization of the electronic structure, the perturbation treatment would no longer be applicable. In order to investigate the energetics and the electronic features of the dimer, we are using molecular orbital methods which account for all electrons in the system.

R. Sayre, J. Smith, J. Harlos and R. Rein

# INDIVIDUAL REPORTS

# INDIVIDUAL REPORT - MONOMOLECULAR FILM STUDY GROUP

D. A. Cadenhead

1. DEFINITION OF FIELD OF INTEREST:

   a) Characterization of monolayer properties (air-water interface) of various membrane lipid components and related molecules.

   b) Studies of molecular interactions in mixed monomolecular films.

   c) Evaluation of film-substrate interactions.

2. FINANCIAL SUPPORT:

Financial support during 1968 came from NASA, NGR 33-015-016 and NIH Grant GM 11603-05 (latter terminated August 31, 1968)

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| D. A. Cadenhead | Working Party Chairman, Associate Professor, Chemistry |
| Judith Csonka | Technician -Full Time Terminated 10/15) |
| Leslie Csonka | Undergraduate Assistant - Part time |

4. RESEARCH PROGRAM:

a) Monolayer Characterization Particular emphasis has been placed on ascertaining those molecular characteristics which establish the physical state of a film (gaseous, liquid-expanded, intermediate liquid-condensed, solid). Among the factors studied have been: the condensing

effect of ether as opposed to ester alkane chain attachment to glycerol, chain length and branching and the behavior of rigid as opposed to flexible amphipathic molecules. Such studies have enabled us to specify that at (say) room temperature, only 1,2-dipalmitoyl-3-lecithin and 1,2-dimyristoyl-3-cephalin in their corresponding homologous series exhibit an isotherm possessing an intermediate region. Based on the failure of rigid amphipathic molecules to exhibit such a region an evaluation was made of the relative merits of the Langmuir and Kirkwood theories concerning the nature of this "phase". The increasing amount of evidence relating this phase in monolayers to liquid crystalline, bilayer and membrane lipid states justifies the effort made in this direction.

b) Molecular Interactions in Mixed Monolayers While studies have been made primarily with systems using cholesterol as a condensing agent, non cholesteric mixed films have also been studied. An evaluation of results based on mean molecular area (and dipole) plots has led us to two definite conclusions:

1. The postulation of "molecular complexes" at compositions corresponding to sharp inflections in molar plots is completely unjustified. Such inflections arise through phase changes in the state of the more expanded monolayer component.
2. In the systems studied by this group, a thermodynamic analysis reveals that the condensation process is exothermic and involves molecular interaction. "Space

filling" as defined by Shah and Schulman may play a partial role.

Present efforts are directed towards establishing an improved and more quantitative parameter $P_c$ "the percent condensation" in the hope that a meaningful comparison can be made of the ability of cholesterol to condense a wide variety of membrane lipids.

c) Film Substrate Interations Where interaction between the aliphatic chains of amphipathic molecules and aqueous substrates are possible, addition of various substrate additives (glycerol, glycol, alcohol, urea) produce enhanced interactions and expansion effects. Coupled with this, there appears to be a reduced ability of the polar groups to orient the substrate molecules (as evidenced by surface potential measurements). When the film is condensed, only the polar group interaction is evident. Such studies have enabled us to evaluate the role of the substrate in establishing the state of a monolayer.

d) Other Studies We have recently completed work on a 3-substituted series of β-estradiols in an attempt to correlate the behavior of such molecules at the air-water interface (a crude membrane-like model environment) with their estrogenic hormonal activity. The results are presently being evaluated. An attempt to develop a quantitative interpretation of surface potential data including the substrate contribution has been initiated.

5. PUBLICATIONS:

1. "Monomolecular Films: Films of Phospholipids and Films on Aqueous Glycerol Substrates," R.J. Demchak, PH.D. Thesis, February, 1968
2. "Molecular Interactions in Mixed Monolayers," D.A. Cadenhead and M.C. Phillips, Advances in Chemistry Series (A.C.S. Publications) "Molecular Interactions in Biological and Related Systems". (1968)
3. "The Intermediate State: A re-evaluation," D.A. Cadenhead and R.J. Demchak, J. Chem. Phys., 49, 1372 (1968)
4. "Molecular Interactions in Monomolecular Films: a New Representation Part I Cholesterol and Elaidic Acid," D.A. Cadenhead and R.J. Demchak, J. Colloid. and Interface Sci., in press.

6. MEETINGS AND PRESENTATIONS:

1. "Cholesterol-Phospholipid Interactions" Invited talks, Universities of Leiden and Utrecht, The Netherlands, June, 1968
2. "Monolayers of Biological Significance" Invited talk, Chelsea College of Arts and Science, London, England, July, 1968
3. "The Physical States of Monomolecular Films" Invited talk, Gordon Research Conference On Interfaces, Meriden, New Hampshire, July, 1968

7. CONTRIBUTIONS TO UNIVERSITY TEACHING: (D. A. Cadenhead)

a) Undergraduate Physical Chemistry (Chem. 319-320L)

b) Surface Chemistry for Graduate Students (Chem. 534)

c) 1968 Chairman of Educational Committee of the American Chemical Society Division of Surface and Colloid Chemistry.

# INDIVIDUAL REPORT - SURFACES AND MEMBRANES

R. J. Good

## 1. DEFINITION OF FIELD OF INTEREST:

Theory of interfacial tension.

## 2. FINANCIAL SUPPORT:

a) NSF GK 1985

b) Allied Chemical Corp.

c) (Up to June 30, 1968) Phillips Petroleum Co.

d) (Up to Aug. 31, 1968) Center for Theoretical Biology (fellowship for Dr. Elbing)
NGR 33-015-016

## 3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| R. J. Good | Professor, Chemical Engineering, Surface Chemistry and Physics |
| E. Elbing | Chemical Engineering |

## 4. RESEARCH PROGRAM:

(a) Theory of Interfacial Tension: The theory of interfacial tension which has previously been developed, relating to intermolecular forces, has been carried nearly to completion. Some new contributions have been: the use of the Kihara "core" potential for dispersion forces, and the distinction from dipole-dipole forces which do not follow a Kihara form of potential; this treatment has vastly improved the fit of theory to data on both nonpolar

and polar liquids vs. water. Another novel result is an estimate of the strength of a hydrogen bond across an interface. For benzene vs. water, it is about 2 kcal/mole.

(b) Experiment: Interfacial tension at 1 atm. pressure. An attempt has been made with apparent success at establishing the first primary standard for liquid-liquid interfacial tension. For benzene vs. water, it is 33.9 ergs/$cm^2$ at 20°C. which was obtained by two independent methods. This result revises the formerly accepted result of Harkins and Brown. The temperature coefficient was also measured by both methods.

The time-dependence of interfacial tension was also studied. Traces of surface active material (such as stearic acid) in the $10^{-5}$ molar range, dissolved in benzene, cause a rapid decrease in interfacial tension, eg 0.1 dyne/cm per minute. This is a stronger effect than would be expected from known diffusion coefficients.

(c) Interfacial tension at high pressure: The high pressure equipment has been put into operation, and preliminary results for the pressure coefficient of the interfacial tension for benzene vs. water are being obtained currently.

5. PUBLICATIONS, PAPERS AND SEMINARS:

(i) "Anisotropy of Contact Angles on Stretch-Oriented Polymers", San Francisco ACS Meeting, April, 1968.

(ii) "Intermolecular Forces in Adhesion", Wayne University Polymer Conference, June, 1968.

(iii) "A New Thermal Effect in Adhesion", Wayne University Polymer Conference, June, 1968.

(iv) "Theory of Interfacial Tension in Systems of High Mutual Solubility", Industrial & Engineering Chemistry Symposium on Surface Chemistry, June, 1968.

(v) "Theory of Interfacial Tension of Polar Liquids", Seminar at Dept. of Chemistry, University of Waterloo, Waterloo, Ont.

(vi) Paper presented, "Thermodynamics of Bilayer Film Formation", ACS Meeting, Atlantic City, Sept., 1968.

(vii) Organized a symposium on "Stability of Thin Films".

6. MEETINGS:

(i) National Colloid Symposium, Chicago, June, 1968.

(ii) Gordon Conference on Chemistry at Interfaces, July,'68

(iii) Gordon Conference on Adhesion, Aug., 1968.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

(i) Eng. 9527 "Colloid & Surface Phenomena", Spring, 1968 (graduate level course)

(ii) Eng. 9534 "Principles of Materials Science", Spring, 1968 (graduate course)

(iii) Eng. 9433 "Materials Science for Chemical Engineers" Fall, 1968-69 (undergraduate)

# INDIVIDUAL REPORT - ESTROGEN RECEPTOR

M. May

1. DEFINITION OF FIELD OF INTEREST:

Estrogen receptor structure and function.

2. FINANCIAL SUPPORT:

NIH GM 11603, HE 09336

NASA NGR 33-015-016

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

| | |
|---|---|
| Marian May | Assistant Professor, Center for Theoretical Biology |
| Fred Ridley | Research Associate Biochemical Pharmacology |
| C. Liarakos | Research Assistant Biochemical Pharmacology |

4. RESEARCH PROGRAM:

A series of 3, and 17 substituted Estradiol analogs have been synthesised by F. Ridley and pharmacologically assayed, as the first step in the development of irreversibly binding analogs for the 17β Estradiol receptor site(s). These substitutions resulted in a marked decrease in estrogenic potency, and intrinsic affinity for the receptor site(s), but similar intrinsic activities were retained as demonstrated by increased dosage, resulting in maximum uterotrophic response. A second binding area in close proximity to the C3-OH estradiol binding area was revealed which may be available for irreversible binding,

and so further the investigation into the localisation and identification of the uterine estrogen receptor site(s). The in vitro uptake of tritium labelled 17β - estradiol by the mouse uterus, and the effect of the substituted estrogens on this uptake indicated that in the case of the 3, alkoxy estra 1,3,5(10)-trien 17β-ols, they were indeed acting at the uterine 17β-estradiolsite. Further investigation of this project has been prevented due to lack of funds.

5. PUBLICATIONS, PAPERS AND SEMINARS:

(see publications under Working Party on Receptor, structure, function and isolation.

C. Liarakos and M. May "The estrogenic activities of some 3-alkoxy-estra-1,3,5(10)-Trien-17β-ols", Endocrinology,1969 (in press)

6. MEETINGS:

None

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

M. May participated in Pharmacology 469, 501 and 503.

INDIVIDUAL REPORT - STATISTICAL MECHANICS

P. B. Bright

1. DEFINITION OF FIELD OF INTEREST:

A. Transport equations in the presence of chemical reactions giving rise to momentum sources and sinks.

B. Irreversibility, continuity, and differentiability.

C. Application of previous results to problems of tracer kinetics.

2. FINANCIAL SUPPORT:

Research supported by Center for Theoretical Biology Funds.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Research Associate, CTB: Research Instructor, Biophysics.

4. RESEARCH PROGRAM:

1) Concerning the "Anisotropic" contribution of chemical reactions to the transport equations and active transport: This paper shows how the momentum sources and sinks resulting from chemical reactions may be rigorously incorporated into the flow equations. It is still based on a concept of intermolecular friction which is widely but not universally accepted. This concept and the concept of diffusion is the subject of the second project.

2) Irreversibility, Continuity and Differentiability: This paper is an extension of a portion of last year's paper on "Mean Return Processes" which was considered too long to publish. The primary objective is to show that the infinitesimal properties of stochastic processes do indeed make noticeable differences on the macroscopic scale. Since last summer it has been the subject of continuing communications with Professor Robert Mazo. Copies have recently been sent to Professors G. Uhlenbeck and Mark Kac at Rockefeller University in anticipation of consultation in the near future.

A second paper showing the relation between the local equations for the evolution of density in phase space for discontinuous, continuous and differentiable processes and their relation to the time evolution of macroscopic observables has been prepared. An extension of this paper to find physical situations which discriminate between these models of velocity is in preparation.

3) The application of the previously derived flow equations to tracer kinetics holds several promises. It should provide greater insight into the relation of macroscopically measured coefficients such as mobility and diffusion coefficients to molecular properties. It should also provide a more general and rigorous basis for the equations of tracer kinetics and the interpretation of tracer studies in the presence of chemical reactions.

5. PUBLICATIONS, PAPERS AND SEMINARS:

Also see Working Party of Models of the Visual Pathway, etc.

1) "Concerning Anisotropic Contributions of Chemical Reaction to Flow Equations and Active Transport", J. Theo. Biol. (in press)

2) Abstract presented to Biophysics Society Annual Meeting, February.

3) Seminar, March 13.

6. MEETINGS:

Also see Working Party of Models of the Visual Pathway, etc.

1) Biophysics Society Annual Meeting, February, Pittsburgh

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

| | | |
|---|---|---|
| Sections of Biophysics: | 401 | - Introduction to Biophysics |
| | 508 | - Mathematical Biophysics |
| Biophysics | 647-8 | - Research |

8. MISCELLANEOUS ACTIVITIES:

Seminar coordinator - CTB

Member: Seminar, Libary and Publications Committee
Academic Committee, elected representative of research associates
Sub-Committee on doctoral training program.

INDIVIDUAL REPORT - SYMBOLIC RELATIONAL SYSTEMS

C. Andrew Hilgartner, MD

1. DEFINITION OF FIELD OF INTEREST:

General semantics; theories of human psychodynamics; symbolic relational systems; logic of science.

2. FINANCIAL SUPPORT:

Center for Theoretical Biology

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Temporary Senior Research Associate, CTB
C. Andrew Hilgartner, M. D.

4. RESEARCH PROGRAM:

Studies of human behavior in small groups.

5. PUBLICATIONS, PAPERS AND SEMINARS:

Hilgartner, C. A., General Semantics, Psychotherapy, and the Logic of Science, etc.: A Review of General Semantics 25: 315-324 (1968)

Hilgartner, C. A. and Randolph, John F.: Psycho-Logics: An Axiomatic System Describing Human Behavior

1. A Logical Calculus of Behavior
2. The Structure of 'Unimpaired' Human Behavior
3. The Structure of Empathy

J. of Theo. Biol. (in press)

Hilgartner, C. A., Chain-Indexing in the Design of Experiments, General Semantics Bulletin, (in press)

6. MEETINGS:

Tenth International Conference on General Semantics, Denver, Colorada, August.

Symposium on Information Processing in the Nervous System, SUNY/B, October.

# V. CONTRIBUTIONS TO THE UNIVERSITY TEACHING PROGRAM

## COURSES OFFERED FROM THE CENTER FOR THEORETICAL BIOLOGY

### Theoretical Biology/Biophysics Course 509R

The course was organized by Dr. A. I. McMullen with the assistance of Drs. Hamann, Leibovic, Rein, Triggle (CTB) and Williams (Biology). It was divided, like Gaul, into three parts:

(I) Spontaneous assembly of macromolecules

A. I. McMullen, R. Rein and R. Williams

(II) Mechanisms of Receptor Action

D. J. Triggle and J. Hamann

(III) Mechanisms of the Central Nervous System

K. Leibovic

The course was attended consistently by a small group of students embracing the disciplines of biology, biochemical pharmacology, mathematics, biophysics and theoretical biology.

### Biophysics 524/Mathematics 541 - R. Rosen

Mathematical Biology; Dynamical Properties of Biological Systems

This course is one of a series aiming at development of the basic mathematical concepts underlying the theoretical study of biological systems, at all levels of biological organization, and illustrated by examples drawn from the entire field of biology. Examples will include such topics as cellular controls and differentiating systems,

regulation of physiological processes, Volterra systems in ecology, etc. The theoretical aspects to be developed are the following: Basic concepts of system description and analysis. Dynamical systems and their properties; stability. Dynamical systems with feedbacks; control systems; adaptive and self-organizing systems. Basic properties of discrete systems; finite automata. Finite automata with feedback; Turing machines and "self-reproducing automata".

Prerequisites: Differential equations, some knowledge of modern algebra.

Lectures on System Theory - R. Rosen
December, 1968

Partly to serve as preparation for this summer's Colloquium on Theoretical Biology, a series of nine lectures was offered reviewing System Theory and its role in biology. These lectures were concerned mainly with continuous systems, but the theory of automata was briefly discussed, and the relation between the continuous-time and the discrete-time formalisms was stressed.

SYMPOSIA PRESENTED - CENTER FOR THEORETICAL BIOLOGY

Symposium -"CORRELATION OF MODEL AND NATURAL MEMBRANE STUDIES"

4248 Ridge Lea, June 26, Dr. A. I. McMullen, Chmn.

Main Presentation: "Recent Physical Studies of Lipids and Biological Membranes" - Dr. D. Chapman

Dr. D. Chapman was visiting professor to the Center during the period 20-27, June. A one day Symposium was held on June 26, on the "Correlation of Model and Natural Membrane Studies".

Dr. Chapman is Professor of Chemistry, Sheffield, England, and of Cambridge (The Cavandish Department). He is also Head of General Research Division of Unilever, Principal Scientist and Head of Molecular Biophysics.

The following short papers were presented at the Symposium:

"The Redetermination of Phase Angles for Small Angle X-Ray Diffraction of Myelin Membrane by Heavy Metal Labeling"
Drs. C.K. Ackers, D.F. Parsons
Department of Biophysics
Roswell Park Memorial Institute

"Glycoprotein Components of Erythrocyte Membranes"
Dr. Richard J. Winzler
Department of Biochemistry, SUNY/B

"A Possible Model of the Necturus Proximal Tubule, its Relationship to Trans-epithelial Osmotic Water Flow"
Dr. Carl J. Bentzel
Department of Medicine, SUNY/B
and Buffalo General Hospital

"Applicability of Goldman's Constant Field Assumption to Biological Systems"
Drs. A.D. MacGillivray and D. Hare
Departments of Mathematics and Biophysics, SUNY/B

Symposium - "FUNDAMENTAL CONCEPTS IN DRUG RECEPTOR INTERACTIONS"

SUNY/B, August 26-28, Dr. D. J. Triggle, Chmn.

A symposium entitled "Fundamental Concepts of Drug-Receptor Interactions" was held on August 26-28. This meeting was sponsored jointly by the Institute of Pharmacology, University of Milan and the School of Pharmacy, SUNY/B. The meeting was attended by approximately 180 people.

The basic principle of this meeting was to discuss drug-receptor interactions from several points of view since it now seems quite clear that this multifaceted approach has the most to offer. It was also decided to have a relatively small number of presentations in order to allow each speaker a reasonable time to develop his theme and, most importantly, to allow adequate time for discussion. This proved to be the case and lively discussions took place after every presentation.

The first presentation was by Dr. Alfred Burger (Dept. of Chemistry, University of Virginia) who discussed the interpretation of structure-activity relationships from the approach of the medicinal chemist. He was followed by Dr. Lemont B. Kier ( Dept. of Biochemistry, Battelle Memorial Institute, Columbus, Ohio) who spoke on the application of M.O. techniques to the determination of preferred conformations and charge distributions in biologically active molecules. The basic assumption in this treatment is that information will thus be obtained

concerning the (presumed) complementary macromolecular binding surface.

In the afternoon attention turned to the interpretation of drug-receptor interactions in terms of enzyme models. B. Belleau (Dept. of Chemistry, University of Ottawa) discussed a thermodynamic analysis of the binding of quaternary ammonium ligands to acetylcholinesterase and the extrapolation of these data to the acetylcholine (muscarinic) receptor. T. R. Podleski (Pasteur Institut, Paris) spoke of an allosteric model of the acetylcholine receptor developed by him and J. P. Changeux. The basic feature of this model (based on evidence from the cholinergic receptor of the electric organ of the electric eel) is the cooperative interaction of the ligand binding sites which are also presumed to be membrane sub units.

On the second day, the first presentation was by Dr. G. A. Robison (Dept. of Pharmacology, Vanderbilt University) who discussed the general role of cyclic AMP as a second messenger common to the action of many hormones. Dr. S. Dikstein (The Hebrew University, Jerusalem) then spoke of the biochemical relationships involved in the events of stimulus, response and recovery of the biological system, his thesis being the primary roles played by ATP, ADP and $Ca^{++}$.

The third presentation of the second day was by Dr. L. E. Hokin (Dept. of Pharmacology, University of Wisconsin) who discussed the purification of the $Na^{+}$, $K^{+}$, ATPase and its potential role as the receptor for cardio active

steroids such as ouabain and stropanthidin. Dr. J. Gorski (Dept. of Physiology, University of Illinois) then discussed the sites and mechanisms of action of the estrogenic hormones, developing the concept that there are at least two macromolecular binding sites involved; one site involved in the cytoplasmic transport of the hormone and the other involved in the nuclear binding of the molecule.

On the final day W. D. Stein (Dept. of Biological Chemistry, University of Manchester) spoke on the isolation of permeases, those membrane bound macromolecular constituents concerned with the translocation of material (i.e. sugars) across the cell membrane. This work is primarily concerned with E.coli, where the possibility of ready genetic manipulation has made possible elegant experiments on the isolation of involved proteins. Finally, J. F. Moran (Dept. of Biochemistry, SUNY/B) spoke on the quantitation of adrenergic and cholinergic receptors. This work establishes the direct relationship between receptor occupation and tissue response in these systems and points out some of the difficulties in studying drug-receptor interactions through use of antagonists.

It was agreed that the symposium had been successful in its avowed aim of presenting some of the different approaches to the analysis of drug-receptor interactions. In his concluding remarks, J. F. Danielli (CTB, SUNY/B) emphasised the general conclusion of the symposium that greater emphasis must be paid to the problems of isolation of receptor constituents.

Symposium - "INFORMATION PROCESSING IN THE NERVOUS SYSTEM"

SUNY/B, October 21-24, K. N. Leibovic

This Symposium was organized by the CTB, SUNY/B and the Center for Visual Sciences, University of Rochester, in cooperation with the Dr. John C. Eccles Laboratories of Neurobiology, and the Departments of Biophysical Sciences, Mathematics and Computer Sciences at SUNY/B.

PROGRAM

Monday, October 21,

I. Linguistics Theories in Relation to CNS Operation

| | |
|---|---|
| W. A. Wickelgren, Chairman | MIT |
| P. S. Peters, speaker | U. of Texas |
| A. M. Liberman, speaker | U. of Connecticut |

II Automata Theory

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|---|---|
| M. Arbib, Chairman | Stanford U. |
| H. C. Longuet-Higgins, speaker | Edinburgh U. |
| R. Rosen, speaker | SUNY/B |

Tuesday, October 22,

III Psychophysiology

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|---|---|
| R.M.Boynton, Chairman | U. of Rochester |
| R. Haber, speaker | U. of Rochester |
| P. Schiller, speaker | MIT |
| M. Clynes, speaker | Rockland State Hosp. |

IV Anatomy and Physiology

| | |
|---|---|
| W. A. H. Rushton, Chairman | Cambridge U. |
| H. B. Barlow, speaker | U. of California, Berk. |
| R. M. Boynton, speaker | U. of Rochester |

Wednesday, October 23,

V. Anatomy and Physiology (continued)

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|---|---|
| J. C. Eccles, speaker | SUNY/B |
| V. B. Brooks, speaker | NY Medical College |

VI. Models and Theory

| | |
|---|---|
| Otto Schmitt, Chairman | U. of Minnesota |
| W. S. McCulloch, speaker | MIT |
| R. F. Reiss, speaker | Palo Alto, Calif. |
| K. N. Leibovic, speaker | SUNY/B |

Thursday, October 24,

VII. Final Synthesis and Stock Taking

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|---|---|
| K. N. Leibovic, Chairman | SUNY/B |
| W. A. Wickelgren, speaker | MIT |
| M. Arbib, speaker | Stanford U. |
| R. M. Boynton, speaker | U. of Rochester |
| W. A. H. Rushton, speaker | Cambridge U. |
| Otto Schmitt, speaker | U. of Minnesota |

SEMINARS PRESENTED - CENTER FOR THEORETICAL BIOLOGY

Seminars held at the Center for Theoretical Biology and the abstracts as they appeared on the notices:

January 11, 1968 — Dr. John A. Howell
Chemical Engineering Department, SUNY/B

A MODEL FOR THE SYNCHRONOUS GROWTH OF MICRO-ORGANISMS

A simple two-variable model has been constructed to describe the synchronized growth of micro-organisms. It can be used to indicate a possible method for growing organisms in a continuous reactor so that they are at different stages of the life cycle in different regions of the reactor rather than at different times.

January 18, 1968
January 19, 1968 — Dr. Stephen Grossberg
Department of Mathematics
Massachusetts Institute of Technology

A NEW LEARNING THEORY WITH PHYSIOLOGICAL IMPLICATIONS

This was a joint seminar sponsored with the Mathematics and Biophysics Departments.

Nonlinear networks will be developed from simple psychological ideas which contain analogs to neurophysiological structures and processes. The networks learn, remember, and recall in a satisfying "psychological" way. Facts about various learning paradigms are then clear by inspection. Theorems show how the geometry of the networks influences their learning. If time permits the continued psychological derivation leads to more "neural" systems

that exhibit lateral inhibition and thresholds, which reduce to the Hartline-Ratliff equation in the simplest case, and which provide a series of heretofore unmeasured physiological predictions along the way.

January 25, 1968 — Dr. Robley Williams
N.I.H. Post-doctoral Fellow, Biology, SUNY/B

NON-COVALENT ASSOCIATION OF A DECAPEPTIDE

The association in an aqueous solution of the cyclic decapeptide, tyrocidine B, will be discussed. Experimental measurements of stoichiometries and association constants by equilibrium ultracentrifugation will be presented.

February 1, 1968 — Dr. Gerald F. Doebbler
Linde Division-Union Carbide

INHIBITION OF ENZYME SYSTEMS BY INERT GASES

Metabolically inert gases, including the noble gases, have been shown to produce a variety of biological effects at elevated pressures. The heavier inert gases inhibit various enzyme reactions, the kinetics of which suggest an allosteric nature of the inhibition.

February 8, 1968

Dr. Robert M. Boynton
Professor of Psychology and Optics
Director, Center for Visual Science
University of Rochester, New York

ON THE DISCRIMINATION AND RECOGNITION OF COLOR

The adaptive significance of chromatic vision is considered. Chromatic vision allows for the discrimination of borders and details that would otherwise be invisible at near-equal luminance, but it also permits the evaluation of large patches of color on an absolute basis (recognition). Experimental data will be presented and evaluated; it will be concluded that chromatic vision usually aids recognition more than discrimination.

February 9, 1968
Special
Seminar

Dr. Joost Manassen
Plastics Research Laboratory,
Polymer Department
Weizmann Institute of Science
Rehovoth, Israel

METAL PORPHYRINS AND PHTHALOCYANINES AS CATALYSTS IN CHEMICAL REACTIONS

Organic polymers as well as metal organic compounds have been shown to be active as catalysts in vapor phase reactions under certain conditions. With metal porphyrins and phthalocyanines, it has been possible to find a correlation between the electronic structure of the complex and its catalytic activity.

February 15, 1968 — Professor Aldo Rescigno
Department of Physical Biochemistry
John Curtain School of Medical Research
Australian National University

DO COMPARTMENTS EXIST IN NATURE?

The concept of Compartment has been widely used and several definitions of it have been given in the literature. No single definition is completely satisfactory, nevertheless the interpretation of biological systems in terms of Compartments has a great practical and heuristic value.

February 22, 1968 — Professor John H. Milsum
Director, BioMedical Engineering Unit
McGill University, Montreal, Quebec

ON OPTIMIZATION IN BIOLOGICAL CONTROL SYSTEMS

Biological control systems may be optimized on two bases; first, the design optimization with regard to structure of the system and secondly, an operating optimization to minimize some relevant performance criterion. Evidence is increasing that the performance criterion for operating optimization relates to plausible factors such as energy utilization. Posture, locomotion, respiration and neuromuscular reflexes are considered in this regard.

February 29, 1968 — Dr. David J. Triggle
Departments, Biochemical Pharmacology and Biophysics; and the Center for Theoretical Biology, SUNY/B

THE QUANTITATION OF PHARMACOLOGICAL RECEPTORS

Some general approaches to the analysis of the structure and function of pharmacological receptors will be discussed, including approaches to the direct isolation of receptor material. The implication of these findings in relation to

the analysis of one relationship between receptor occupancy and physiological response will be discussed.

March 7, 1968 — Dr. Carl Gans
Professor of Biology, SUNY/B

RELATIVE SUCCESS OF DIVERGENT PATHWAYS IN AMPHISBAENIAN SPECIALIZATION

Animal groups vary in the number, range, and population density of their component species. The superficially most specialized forms are often least "successful" in terms of these criteria. This general problem, and some functional states possibly affecting it, will be considered for the Amphisbaenian, a suborder of burrowing reptiles.

March 14, 1968 — Dr. G. R. Blakley
Department of Mathematics, SUNY/B

NATURAL SELECTION ACTING ON POPULATIONS AT LOW DENSITY or/at HIGH DENSITY

When randomly seasonally mating populations at low density are subject to selection, their growth rates increase. At high density or when genotypic fitness is nonconstant, this need not happen. Stability of balanced polymorphism will be discussed.

March 21, 1968 — Dr. Donald F. Parsons
Department of Biophysics
Roswell Park Memorial Institute

Dr. Robert Rosen
Departments, Biophysics and Mathematics
SUNY/B

Dr. Peter B. Bright, Moderator
Department of Biophysics
SUNY/B

PANEL DISCUSSION

Do we have the right balance in the Teaching, Research, and University Structures between Theory and Experiment?

From the present state of development of the biomedical sciences some would call for greater emphasis on the collection of further experimental data while others would call for greater emphasis on the evaluation of data already at hand. In striving for greater yield from scientific efforts one seeks criteria for predicting relative cost-effectiveness judgments between alternative proposed programs.

March 28, 1968 — Dr. Irving Biederman
Assistant Professor of Psychology, SUNY/B

PARALLEL VS. SEQUENTIAL PROCESSES IN PERCEPTUAL RECOGNITION

A series of experiments will be reviewed and a model advanced for the way in which humans recognize multidimensional visual stimuli. A central issue in this research is whether the processes intervening between stimulus and response proceed in a parallel or sequential fashion.

April 8, 1968
Special
Seminar

Dr. Alex Comfort
University College
London, England

PREVENTION OF AGEING IN CELLS

A special seminar co-sponsored by Department of Biology and The Center for Theoretical Biology.

April 11, 1968 — Dr. G. S. Manning
Assistant Professor Rockefeller University
New York, New York

ON THE KINETIC BASIS FOR OSMOTIC FLOW THROUGH LEAKY MEMBRANES

An analysis of binary diffusion and bulk flow through a potential energy profile shows that the Kedem-Katchalsky flow equations are inherent in such a model. The role of the pressure gradient as the driving force for osmotic flow is made evident.

April 18, 1968 — Dr. Marvin Zelen
Department of Statistics, SUNY/B

SOME MATHEMATICAL PROBLEMS ASSOCIATED WITH THE CLINICAL SCREENING OF POPULATIONS

A chronic disease may be regarded as being in a pre-clinical state followed by a clinical state. Screening procedures are examinations where the pre-clinical state of the disease is discovered. A theoretical model will be discussed describing the relationship between screening strategies and shorter time to diagnosis.

April 25, 1968 — Dr. Leslie E. Blumenson
Associate Cancer Research Scientist
Roswell Park Memorial Institute, Buffalo

ON THE GROWTH AND FORM OF CANCER OF THE UTERUS

Random walk (diffusion) of cells and local vascular dissemination are two processes contributing to the spread of many cancers. This suggests a class of mathematical models for approximating both the shape of the tumor and its mode of spread.

April 26, 1968
Special
Seminar

Professor Michael Anbar
Division of Exo-Biology
NASA Ames Research Center; and
Weizmann Institute of Science,
Rehovoth, Israel

THE POSSIBLE ROLE OF SONO-CHEMICAL PROCESSES IN MOLECULAR EVOLUTION

The prevailing theory of energy input by electrical discharge, photolysis and radiolysis will be critically reviewed. The mechanisms of sonolysis - the chemical changes in liquid subjected to mechanical action - will be discussed. Evidence that sonolytic processes might have been the major pathway for the formation of the bio-organic matter in the primordial ocean will be presented.

May 2, 1968

Dr. Edward Koenig
Department of Physiology, SUNY/B

THE AXON AS A HEURISTIC MODEL FOR STUDYING EXCITABLE MEMBRANE PROTEIN SYNTHESIS

The axon, lacking the usual protein synthesizing machinery of the cytoplasm (i.e., ribosomes), provides a means for studying a specialized machinery that is associated with the axolemma, and which appears to be concerned with membrane protein synthesis.

May 9, 1968

Professor N. Rashevsky
Mental Health Research Institute
University of Michigan
Ann Arbor, Michigan

NEW CONCEPTS IN MATHEMATICAL BIOLOGY

May 16, 1968

Dr. Daniel Fiat
Head of Nuclear Magnetic Resonance Research
Weizmann Institute of Science
Rehovoth, Israel

NUCLEAR MAGNETIC RESONANCE AND SOME OF ITS APPLICATION TO BIOLOGY

Nuclear magnetic resonance theory and some of its biological applications will be reviewed and in particular hydration and solvation of ions and of metal porphyrins will be discussed.

May 23, 1968

Dr. Jay A. Mann
Department of Chemistry
University of Hawaii

DYNAMIC FORCE BALANCE IN ULTRA-THIN FILMS

The visco-elastic properties of films has been viewed as a boundary condition on the 3D equations of motion or as a 2D motion coupled to the substrate. The first view point as presently formulated yields nonsense in the "membrane limit". The second viewpoint is developed for a membrane flexing with a small amplitude to wavelength ratio and compared to experimental results.

June 6, 1968

Drs. James P. Isaacs and John C. Lamb
Medical Scholars with the Lenora and
Alfred R. Glancy Foundation
Atlanta, Georgia

ON COMPLEMENTARITY IN BIOLOGY: QUANTIZATION OF MOLECULAR MOTION

The new proposition to be offered is that the phenomenological conditions under which minimally essential classes of processes occur in living units are such that the uncertainty product of conjugate variables of molecular motion is enlarged at ordinary temperatures and pressures.

June 13, 1968
Special
Seminar

Dr. Vittorio Luzzati
Centre National de la Recherche Scientifique
Laboratoire de Genetique Physiologique
91 Gif-Sur-Yvette, France

LIPIDS AND MEMBRANES

June 13, 1968

Dr. Allen E. Blaurock
Post Doctoral Fellow, NIH
Institute of Neurological Diseases and
Blindness, King's College, London

AN ELECTRON DENSITY PROFILE OF THE MYELIN MEMBRANE

A theory of X-ray diffraction from a Lamellar Crystal which swells by intercalated layers of fluid has been developed. The theory has been applied to diffraction patterns of nerve myelin sheath swollen in solutions with varying electron density. Following the theory it is possible to give a model electron density profile of myelin in which the absolute values of electron density are specified along with linear dimensions.

June 20, 1968

Dr. Robert Guthrie
Research Associate Professor
Department of Pediatrics,
Childrens' Hospital, Buffalo, New York

INBORN ERRORS OF METABOLISM

Background of subject of human inherited enzyme deficiencies, especially those causing preventable forms of mental retardation, if detected early and treated. Bio-chemistry, Genetic, Public Health, and philosophical considerations of attempts to test all newborn infants for as many of these diseases as possible. At least 100 different diseases exist today, and more are being discovered at a rapid pace.

August 2, 1968

Dr. A. Scheludko
Professor, University of Sofia;
Member, Bulgarian Academy of Sciences
Sofia, Bulgaria

STUDIES OF THIN LIQUID FILMS

Professor Scheludko will describe the original technique which he has developed for the study of thin liquid films. He will illustrate some of the results obtained by means of movies and slides and discuss their theoretical interpretation.

August 12, 1968
Special
Seminar

Dr. Mollie Levine
Department of Biochemistry
University of Manchester, England

SUGAR TRANSPORT ACROSS ERYTHROCYTE CELL MEMBRANES

September 26, 1968

Dr. John Abernethy
Research Instructor
CTB - SUNY/B

FEEDBACK CONTROL ON THE RETINA

The psychophysical phenomena of adaptation and flicker are the end products of a multistage process. The problem of assigning a particular role to a particular anatomical site has been approached by modeling the bipolar-amacrine-ganglion cell complex stationed at the output of the retina to see what function this stage might play. The model is non-linear and utilises a generalised synaptic transfer function to include the bipolar-amacrine feedback loop and lateral interaction via the amacrine system.

October 3, 1968 — Dr. Y. Michaeli
Senior Scientist
Weizmann Institute of Science
Rehovoth, Israel

ION BINDING AND CRITICAL PHENOMENA IN POLYELECTROLYTE SYSTEMS

Seminar co-sponsored by Department of Biophysical Sciences and Department of Chemistry.

October 4, 1968
Special Seminar — Professor Ludwig von Bertalanffy
Department of Zoology
University of Alberta, Edmonton, Canada

WHERE IS GENERAL SYSTEMS THEORY TODAY

October 17, 1968 — Dr. C. A. Hilgartner
Temporary Senior Research Associate
CTB - SUNY/B

$MYTH_1$ AND THE TRAPEZOIDAL WINDOW

Using a logical calculus of behavior (algebraic set theory), I examine the neurobiological events which occur when a human organism encounters a contradiction between what he expects and what he observes, and consequently changes his premises.

October 31, 1968 — Dr. Kwang W. Jeon
CTB - SUNY/B

CELL HEREDITY STUDIES IN AMOEBAE

The nuclear genome of free-living amoebae should be stable, since there are no sexual processes throughout their entire life cycle and the genome is probably polyploid. However, the characters of amoebae have been observed to change both spontaneously and experimentally. Some experimental results on these character changes will be presented together with possible implications.

November 7, 1968

Dr. Petr Hochmann
Institute of Physical Chemistry
Czechoslovak Academy of Sciences, Prague;
Visiting Scientist,
Department of Biophysics
Michigan State University, East Lansing

CALCULATIONS OF SOME GROUND STATE AND EXCITED STATES PROPERTIES OF CONJUGATED ORGANIC MOLECULES BY SEMIEMPIRICAL LCI METHOD

The possibility is discussed of calculating the first ionisation potential, the ground state equilibrium bond lengths and the excitation energies by semiempirical LCI method using the unique set of parameters. Numerical applications are made for the conjugated hydrocarbons.

November 14, 1968

Dr. Ta-You Wu
Professor of Physics
SUNY/B

ON THE NATURE OF THEORIES OF MICROSCOPIC AND MACROSCOPIC PHENOMENA

The basic distinction between the theories of the irreversible phenomena on the macroscopic scale and the theories of the reversible atomic phenomena is emphasized.

December 3, 1968
Special
Seminar

Professor N. Rashevsky
Mental Health Research Institute
University of Michigan, Ann Arbor

PERIODICITIES IN BIOLOGICAL SYSTEMS

December 5, 1968

Professor N. Rashevsky
Mental Health Research Institute
University of Michigan, Ann Arbor

MATHEMATICAL BIOLOGY OF RIOTS BY OPPRESSED GROUPS

## SPECIAL LECTURES - CENTER FOR THEORETICAL BIOLOGY

One day conference - "WHAT ASPECTS OF SCIENCE ARE OF INTEREST TO THE NON-SCIENTIST?"

4248 Ridge Lea Road, February 4, 1968

Dr. Harry Hoff, consultant to the British Atomic Energy Authority and a well known novelist, Dr. Ernest Pollard, chairman of Biophysics at Pennsylvania State University, and Dr. Herman Rahn, chairman of Physiology at SUNY/B, were the guest speakers.

Series of six lectures - "PRESENT DAY THEORY OF THE ELECTRICAL DOUBLE LAYER"

I The Classical Basis of the Theory
II Scope and Limitations
III Applications to Monolayer and Biological Systems

"THE FREE ENERGY OF THE ELECTRICAL DOUBLE LAYER"

I Derivation and General Properties
II Application to the Interaction of Colloidal Particles
III Application to Monolayers, Polyelectrolytes and Related Systems

Acheson Hall, August 8-22, 1968

Dr. Samuel Levine
University of Manchester, England
Visiting Professor at SUNY/B

In these lectures, Dr. Levine concentrated on the physical aspects of the subject and kept the mathematics to a minimum. The lectures were designed for chemists, biophysicists and theoretical biologists.